AN OBESERVATIONAL STUDY COMPARING THE RECOVERY TIME IN PATIENTS RECEIVING ADDITIONAL ANTICONVULSANT DOSE VS THOSE RECEIVING REGULAR DOSE DURING SUPRATENTORIAL CRANIOTOMY.

Dissertation submitted in partial fulfillment of the requirement of the Tamil Nadu Dr. M. G. R. Medical University for the M.D Branch X (Anaesthesiology) Examination to be held in April 2016

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Dissertation submitted to the

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In partial fulfillment of the requirements for the degree of

MASTER OF MEDICINE

IN

ANAESTHESIOLOGY

By

ROSEN ROY MATHEW

Register Number: 201420361

DEPARTMENT OF ANAESTHESIA

CHRISTIAN MEDICAL COLLEGE

VELLORE

APRIL 2016

CERTIFICATE

This is to certify that "**AN OBESERVATIONAL STUDY COMPARING THE RECOVERY TIME IN PATIENTS RECEIVING ADDITIONAL ANTICONVULSANT DOSE VS THOSE RECEIVING REGULAR DOSE DURING SUPRATENTORIAL CRANIOTOMY"** is the bonafide work of Dr. Rosen Roy under my supervision in the department of Anesthesia, Christian Medical College, in partial fulfillment of the requirements for the M.D Anesthesiology Examination Branch X of the Tamil Nadu Dr. M.G.R Medical University to be held in April 2016 and no part thereof has been submitted for any other degree.

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Professor

Department of Anesthesiology

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28/09/2015

CERTIFICATE BY THE HEAD OF THE DEPARTMENT / PRINCIPAL

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DECLARATION

I , Rosen Roy Mathew, do hereby declare that the dissertation entitled “An observational study comparing the recovery time in patients receiving additional anticonvulsant dose versus those receiving regular dose during supratentorial craniotomy” is a genuine record of research done by me under the supervision and guidance of Dr.Ramamani Mariappan, Professor, Department of Anesthesia, Christian Medical college, Vellore and has not previously formed the basis of award of any degree, diploma, fellowship or other similar title of any university or institution.

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An observational study comparing the recovery time in patients receiving additional anticonvulsant dose Intraperatively those receiving regular dose during supratentorial craniotomy.
Dr. Rosen Roy Mathew, PG Registrar, Dr. Ramamani M, Anaesthesiology, Ms. S. Janani Iswarya, Clinical Biochemistry. Dr. Visalakshi, Biostatistics, CMC, Vellore.

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Dear Dr. Rosen Roy Mathew,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

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Dear Dr. Rosen Roy Mathew,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "An observational study comparing the recovery time in patients receiving additional anticonvulsant dose Intraoperatively those receiving regular dose during supratentorial craniotomy" on January 12th 2015.

The Committees reviewed the following documents:

1. IRB Application format
2. Curriculum Vitae' of Drs. Rosen Roy Mathew, Dr. Ramamani, Ms. S. Janani Iswarya, Dr. Visalakshi.
3. Informed consent form (English, Tamil, Hindi, Telugu & Bengali)
4. Information Sheet (English, Tamil, Hindi, Telugu & Bengali)
5. Data Sheet
6. Permission Letters
7. No of documents 1 – 6

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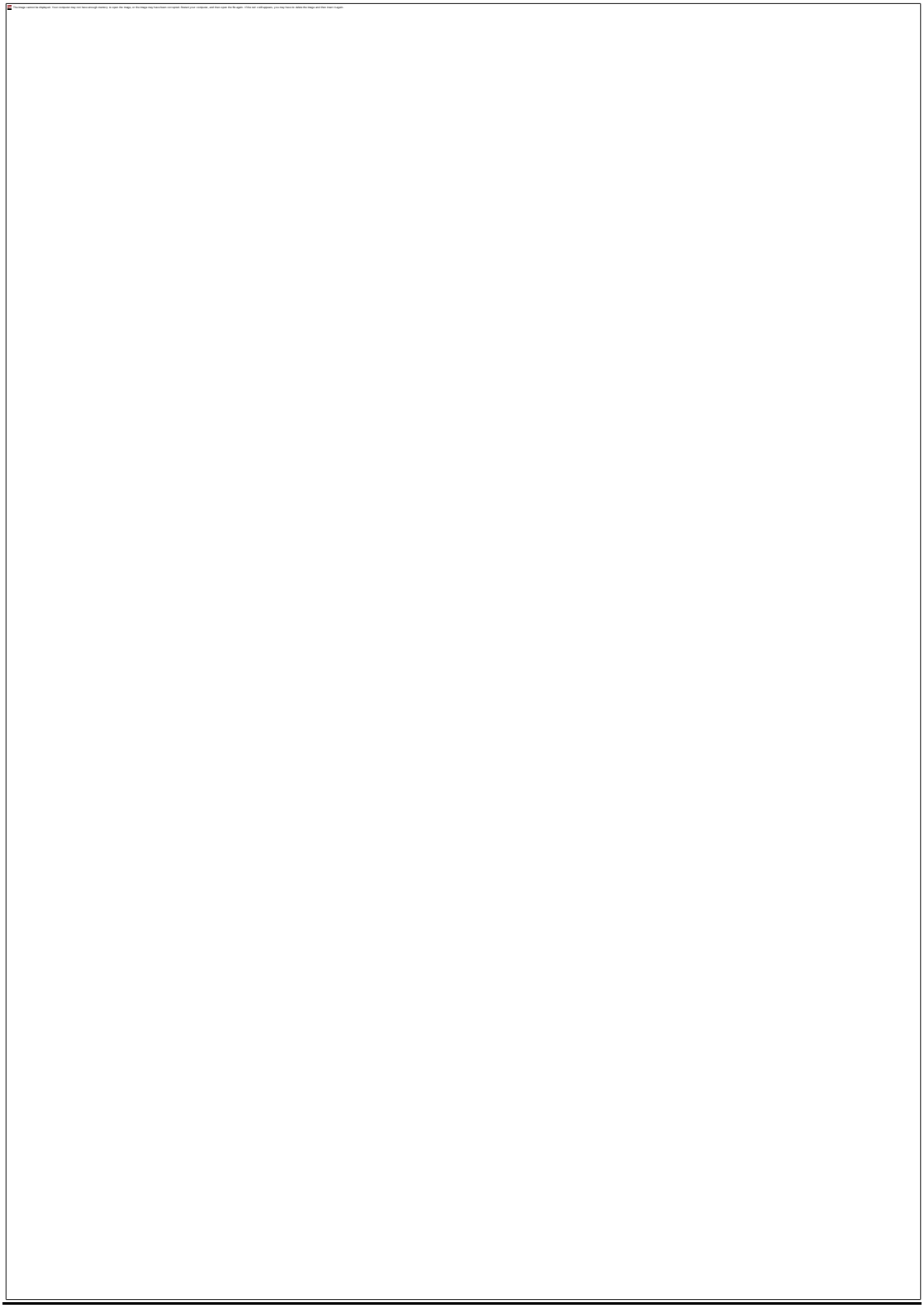

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Yours sincerely

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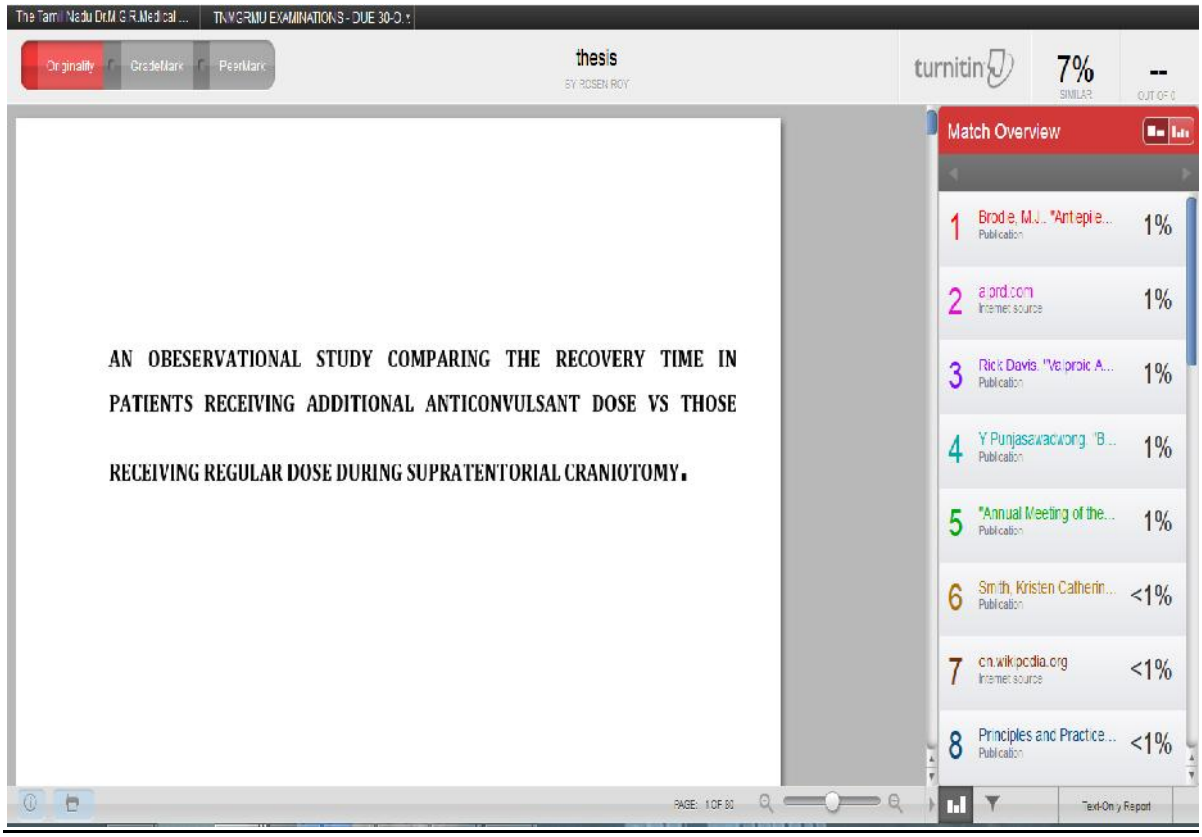
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Rosen Roy Mathew

ABSTRACT

Background and objectives:

This study was done to assess effect of additional anticonvulsant dose given during supratentorial craniotomies on recovery time, haemodynamics, depth of anesthesia, incidence of post operative seizures within 48 hours and plasma anticonvulsant levels. This study enabled us to compare these factors in patients receiving the regular dose of anticonvulsant with additional bolus dose of anticonvulsant.

Patient and Methods:

After getting approval from the Institutional Review Board (IRB) and Ethics Committee of our institution, this study was carried out. After getting informed patient consent, a total of 36 patients who underwent supratentorial craniotomy who fulfilled the inclusion criteria were recruited for this study. This study recruited patients within the time frame of March 2015- August 2015. Patients were divided into 2 groups, of which one group received the regular dose of anticonvulsant (regular group) and the other received an additional dose (additional group) during surgery.

Patients were assessed preoperatively and anaesthetized according to our standard institutional protocol. Apart from routine noninvasive monitoring, haemodynamics was monitored by using an invasive arterial line and the depth of anaesthesia was monitored using Bispectral index monitor. Anticonvulsant was administered during craniotomy and the haemodynamics and changes in BIS were noted during and 1 hour after administration of the anticonvulsant. Plasma anticonvulsant levels were measured before and after craniotomy. Each patient was followed up till they were fully oriented to time place and person. The specific time periods of cutting anesthetic

agent to extubation, time to open eyes, time to obey commands and time to orientation to time place and person were noted. Patients were followed up for a period of 48hours to note the occurrence of seizures.

Results :

36 patients were studied, 19 patients received regular dose of anticonvulsant whereas 17 received an additional dose during craniotomy. The two groups were comparable in distribution of age, sex, weight, tumor location and tumor pathology. The dose of propofol and fentanyl administered during surgery, duration of anesthesia was comparable. There was no significant difference in recovery time when the 2 groups were analyzed as additional dose (Phenytoin +Valproate) and regular dose (Phenytoin + Valproate) however, the subgroup analysis showed significant delay in recovery especially time to obey commands (>15 min) and time to get orientation (>1 hr) in patients who received an additional dose of phenytoin when compared with those who received the regular phenytoin dose. Though these differences looked clinically very significant it was not statistically significant. Hemodynamic fluctuations were clinically significant in the additional phenytoin group, but not statistically significant. There was marginal decrease in BIS values during administration of anticonvulsants. Plasma anticonvulsant levels had significantly dropped in patients who received regular dose (p 0.004). There was a positive correlation between the amount of intravenous fluid administration and drop in plasma anticonvulsant level. Five out of 36 patients had seizures during the immediate postoperative period. Out of these 5, 4 patients had preoperative seizure. Out of 5 who had post operative seizure, two had sub-therapeutic plasma level. We felt that the occurrence of seizures had no correlation with post operative plasma anticonvulsant levels.

Conclusion:

Administration of additional dose of Phenytoin causes delay in recovery and haemodynamic fluctuation during surgery. Administration of additional dose of sodium valproate did not affect either the recovery time, or the haemodynamics. Presence of preoperative seizures is one of the significant risk factor for developing post operative seizure. Since there is a correlation between the amount of IVF administered, blood loss and the decline in plasma level of anticonvulsant, administration of an additional anticonvulsant in patients who are resuscitated with large amount of IVF will definitely help to restore the plasma anticonvulsant level. Due to the small sample size, it is very difficult to comment on occurrence of post operative seizures and the plasma anticonvulsant level. This warrants larger randomized control trials to see the correlation statistically. This study gave us an insight into a probable reason for delay in recovery post craniotomy.

Keywords: anticonvulsant prophylaxis, brain tumors, phenytoin, Valproate, hemodynamics, bispectral index,seizures.

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INTRODUCTION

Seizures are the most common neurological disorder with a prevalence of 0.5%-1%.(1) Seizures pose devastating complications such as loss of consciousness, aspiration of gastric contents, permanent neurological damage. Anticonvulsants are drugs used to control seizures or to prevent seizures (prophylaxis) in the vulnerable population.

Anticonvulsant use began mainly for therapeutic purposes, to terminate an ongoing episode of seizure. However in the recent past, they have been in use for prophylaxis in patients with brain tumors. In patients with brain tumors who present with seizures, use of an anticonvulsant is rational and also recommended by American Academy of Neurology (2002). Use of anticonvulsants in patients with brain tumors, who do not present with seizures, is still controversial. According to the American Academy of Neurology, the use of anticonvulsants is not recommended, if patients with brain tumours do not present with seizures(2). But still it is used commonly in our country, because of the devastating complications of the seizures during the perioperative period.

As Anaesthesiologists, we administer anticonvulsants, either as the regular dose or an additional dose during the intraoperative period according to the surgeon’s preference. Anticonvulsants may inhibit or induce hepatic enzymes, and therefore alter the blood levels of anaesthetic drugs especially non depolarizing muscle relaxants. They can also decrease the efficacy of

steroids such as dexamethasone, which the patient will receive during the perioperative period to reduce the cerebral edema. Anticonvulsants can also reduce the efficiency of chemotherapeutic agents. Allergic reactions, toxicity and cardiac arrest have been reported with the use of them. It can also interfere with cognition and recovery from anaesthesia especially when they are above therapeutic range(3). Since blood levels are not routinely measured, deficits in cognition and recovery are most often attributed to the residual anaesthetic effect, cerebral edema, surgical handling or surgical complications such as tumour bed haematoma, hence the diagnosis of anticonvulsant toxicity is often misdiagnosed. The possibility of high levels of anticonvulsants as a reason for delayed recovery and for the cognitive dysfunction post craniotomy ought to be considered.

In this dissertation we aspire to observe whether administration of bolus or additional dose of anticonvulsant has an effect on recovery from anaesthesia, haemodynamics, depth of anaesthesia, incidence of post operative seizures and the change in plasma anticonvulsant level during supratentorial craniotomy.

AIMS AND OBJECTIVES

Aim:

To assess whether an additional dose of anticonvulsant given during the intraoperative period affects the recovery time after supratentorial craniotomy.

Objectives:

To assess the effect of prophylactic additional anticonvulsants on

1. Time to recovery from anaesthesia – Primary Outcome
2. Hemodynamic changes
3. Depth of Anaesthesia

} Secondary outcomes

4. Incidence of post operative seizure in first 48hours
5. Plasma anticonvulsant levels

-in patients undergoing supratentorial craniotomy.

Hypothesis

Additional anticonvulsants administered during neurosurgical procedures, cause excessive plasma levels leading to hemodynamic changes, increased sedation and delayed recovery in patients undergoing supratentorial craniotomies.

REVIEW OF LITERATURE

Introduction to Neuroanaesthesia

Providing anesthesia for neurosurgical patients requires a sound knowledge of cerebrovascular anatomy, physiology as well as the impact of anesthetic agents on them. Neurosurgical procedures range from burr holes for extradural hematomas to more surgically challenging excision of tumors and cerebral aneurysm clipping requiring efficient anesthetic management.

The occurrence of brain tumor is a common entity. Brain tumors can classified as primary or secondary depending upon the site of origin. They can be classified as benign or malignant according to their histopathology. They may be further classified into supratentorial or infratentorial according to their location. More than 80% of brain tumors in adults are supratentorial, the commonest being gliomas (36%), meningiomas (32.1%) and pituitary adenomas (8.4%)(4). Approximately fifty percent of the tumors are malignant. The five most common sources of brain metastases are breast, colorectal, kidney, lung and melanoma. As there is no organized brain tumor registry in India, it is difficult to obtain epidemiologic data for our country. Age-adjusted incidence rate of primary brain tumor in India is 3.9 per 100,000 population for males and 2.4 per 100,000 populations for females, with a male preponderance for all histological classification(5).

Apart from the routine preoperative evaluation that we do all cases, neurosurgical cases need documentation of tumor location and size, presence of

seizure and its type, neurological deficits and evidence of raised intracranial pressure. Medications such as anticonvulsants and steroids have to be evaluated and optimized before surgery.

Anesthetic management of supratentorial tumors involves optimization of intracranial pressure. Intracranial pressure is governed by 3 factors- cerebral blood volume, cerebrospinal fluid and brain matter. A rise in any of these entities contributes for a raised intracranial pressure. Cautious induction and intubation to avoid hemodynamic fluctuations is warranted. Drop in blood pressure during induction in a patient with raised intracranial pressure can cause cerebral ischemia. On the other hand, laryngoscopy and intubation can raise the intracranial pressure tremendously leading to cerebral ischemia. During the maintenance phase, hyperosmolar agents such as 20% mannitol or 3% saline are administered for brain relaxation. Steroids and anticonvulsants are administered to reduce the cerebral edema and to prevent seizures respectively. Avoidance of secondary insults to the brain such as hypercapnia, hypoxemia, hypotension or hypertension, hypo- or hyperosmolality, hypo- or hyper glycemia and hyperthermia play a significant role in postoperative outcome.

Pathophysiology of seizures

Seizures are due to atypical firing of neurons at abnormally high frequencies, this result in abnormal movements or experiences in an individual. Epilepsy is a tendency to have repeated seizures. Epileptogenesis is the

pathological process that leads to epilepsy. Irritation of the cortical brain, genetic or metabolic abnormalities contribute to Epileptogenesis.

The risk factors for developing seizures depend on the pathology of the tumor as well as its location. Tumor pathology plays an important role in Epileptogenesis. Typically a low grade glioma has higher incidence of seizures than a high grade glioma(6). The reason for this higher incidence is not fully understood till now. The longer survival rates in low grade gliomas as compared with the high grade gliomas may be the reason for higher incidence of seizures in them. Tumor cells can result in the formation of focal or remote cell changes which are responsible for formation of a seizure focus. Dysembryoplastic neuroepithelial tumors and gangliogliomas are low grade tumors that are most commonly associated with seizures, probably because of the fact that they contain neural tissue. Tumors that do not contain neural tissue may also cause seizure by causing cellular changes such as necrosis, scar tissue formation, edema and hemosiderin deposits. These changes are typically seen in high grade gliomas. Epidermoid tumors though they are benign and surgically easy to remove they are most often complicated by post craniotomy seizures because of release of toxic contents while handling the tumor, which can irritate the surrounding brain matter.

Tumor location also plays a critical role in the development of seizures. Tumors in the cortical grey matter are more prone for developing seizures than those in the infra tentorial region. The closer a tumor is to the motor cortex the more prone it is for developing seizures. Tumor location has an influence on

the type of seizure the patient presents with. For example, tumors in the motor cortex present with focal motor seizures while those in the temporal lobe present with aura of unpleasant smells and sounds. Temporal lobe tumors present with complex partial seizures, parietal tumors present with focal sensory seizures and occipital tumors with visual disturbances.

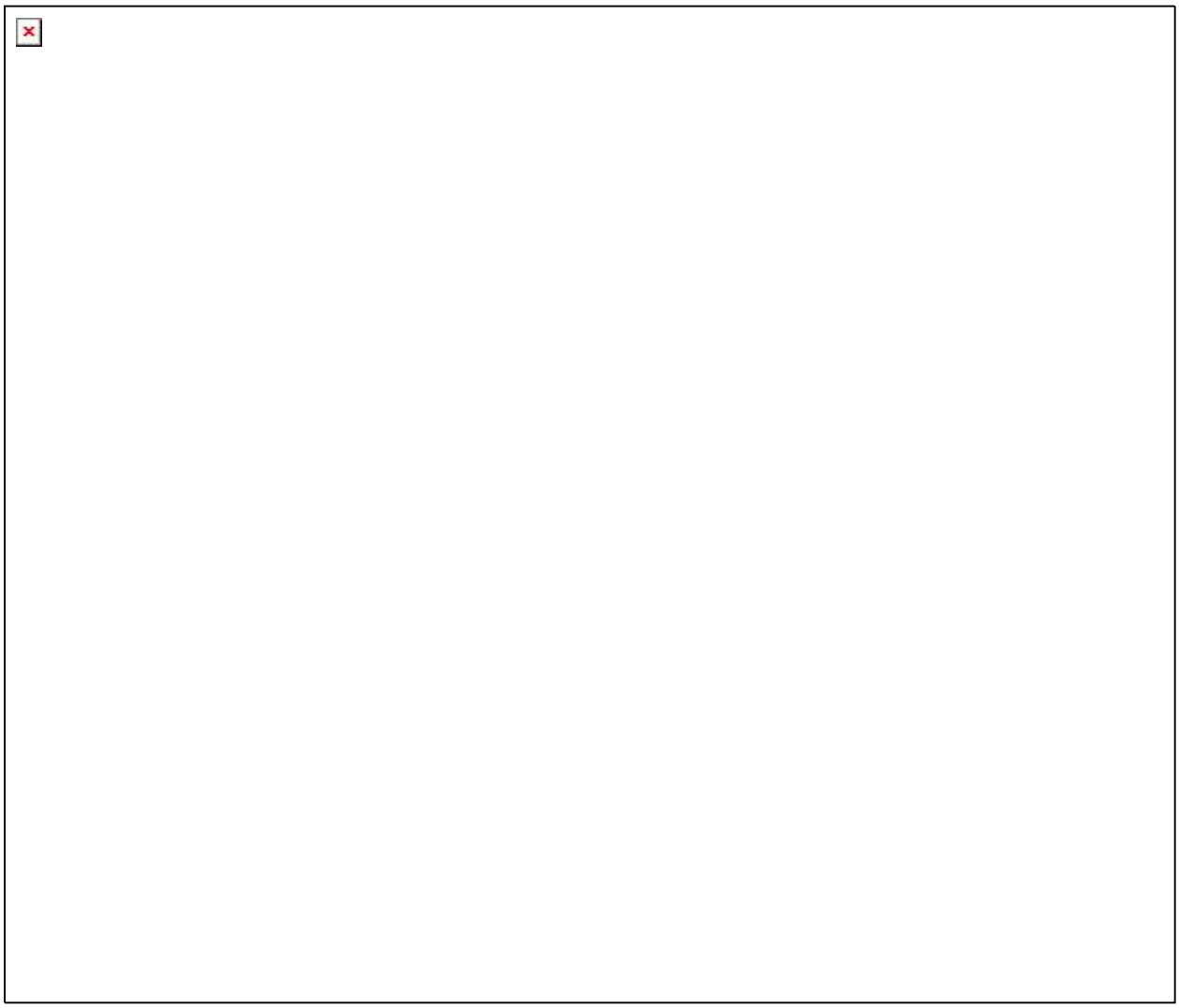


Figure 1: Parts of the Brain and its division into supra and infratentorium by the Tentorium cerebelli.

History of anticonvulsant use in Craniotomies

The beginning of antiepileptic drug use dates back to 11th May 1857, when Charles Locock used potassium bromide to treat 52 cases of hysterical epilepsy. The pharmacological age of anticonvulsants began with the serendipitous discovery of Phenobarbitol by Alfred Hauptmann. He was a psychiatry resident who lived above a ward of patients with epilepsy. Phenobarbitol (luminal) had just begun to be used in psychiatry as a hypnotic drug. Hauptmann sedated his patients with phenobarbitol so he could get a good night sleep as he was continually disturbed by the epileptic patients on the floor below. He subsequently noticed that these patient who he administered Phenobarbitol to, slept well and also had fewer episodes of seizures.

Although Phenobarbitol was effective as an antiepileptic drug it was highly sedative. In 1934 Tracy Putnam along with his colleague Frederick Gibbs experimented with a number of phenyl compounds which were non sedative. They soon discovered Phenytoin. 1936, was the year in which Putnam administered Phenytoin for the first time to Houston Merrit who was an epileptic. Houston Merrit soon became seizure free. More and more drugs were discovered such as troxidone, ethosuximide and Carbamazepine in the middle of the nineteenth century.

Pierre Eymard in 1963 discovered the antiepileptic activity of Valproic acid while he was a resident researcher in the University of Lyon. Extensive

clinical research was done on Valproic acid. In 1967, the sodium salt of Valproic acid was used as an antiepileptic in France.

Benzodiazepines were recognized for the treatment of epilepsy following their synthesis and development by Leo Sternbach, in 1960s. In 1965 Henry Gastaut published a report regarding the efficacy of diazepam in treating status epilepticus. His follow up paper with Clonazepam 6 years later was even more positive. Clobazam is probably the most widely used oral benzodiazepine for a range of refractory epilepsies. Diazepam (rectal and intravenous), midazolam (buccal and intranasal) and Lorazepam(intravenous) are drugs of choice for acute repetitive seizures and convulsive status epilepticus.

The modern era of anticonvulsants began in 1975 when the National Institute of Neurological Disorders and Stroke, United States established the Anticonvulsant Drug Development programme. Over 28,000 chemicals have been studied and developed using target oriented design and structural modification of existing molecules. They all have the ability to decrease neuronal excitation or increase neuronal inhibition by one or more of pharmacological processes, including modulation of voltage-gated cation channels, potentiation of GABAnergic activity, inhibition of glutaminergic processes and modification of release of neurotransmitters.

Pharmacology of phenytoin and sodium Valproate

PHENYTOIN

DESCRIPTION:

Phenytoin sodium is a hydantoin derivative with antiepileptic properties. Phenytoin is also a class Ib antiarrhythmic agent used to treat ventricular arrhythmias. Phenytoin sodium is related to the barbiturates in chemical structure, but has a five-membered ring. The chemical name is sodium 5,5-diphenyl-2, 4-imidazolidinedione, having the following structural formula:(Fig.2)

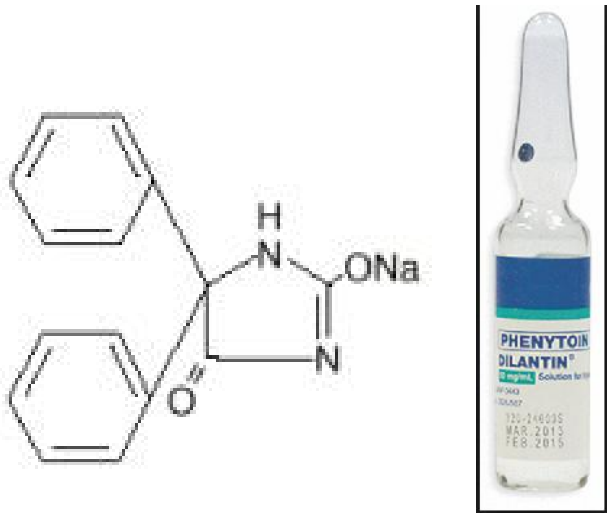


Figure 2: Chemical formula and Intravenous preparation of Phenytoin

MECHANISM OF ACTION:

Phenytoin exerts its antiepileptic action by acting on the motor cortex where it promotes sodium efflux from the neurons. In this way, it tends to stabilize neuronal membranes against hyper excitability. It reduces post tetanic potentiation at synapses and hence prevents cortical seizure foci from

detonating adjacent cortical areas. The brain stem areas responsible for the tonic phase of tonic clonic seizures are maximally inhibited by phenytoin.

PHARMACOKINETICS:

It does not follow linear kinetics (non linear kinetics) as the dose is increased elimination increases up to the point of saturation. The usual therapeutic range is between 10-20 mg/L. Phenytoin is 90% protein bound. It was manufactured as its sodium salt as the absorption is more reliable in this form. Phenytoin is metabolised by cytochrome p450 mixed oxidase and only less than 5 % is excreted unchanged. Its half life is between 10 to 40 hours. Free phenytoin level thus depends on the level of protein therefore in hypo-albuminemia the free concentration increases and can lead to toxicity. Table: 1 shows the conditions in which the free phenytoin levels may increase.

Table 1: Conditions that increase the levels of unbound (free) phenytoin

Insufficient albumin (hypoalbuminemia)	Displacement by endogenous compounds	Displacement by exogenous compounds
Liver disease Nephrotic syndrome Pregnancy Cystic fibrosis Burns Trauma Malnourishment Elderly	Hyper-albuminemia Liver disease Renal dysfunction	Drug interaction: Warfarrin Valproic acid Aspirin NSAIDS (with high protein binding)

DOSE:

Loading dose is 15mg/kg

Maintenance 5-6 mg/kg/day

USES

1. Generalised tonic clonic seizure
2. As an anti arrhythmic
3. Trigeminal neuralgia

THERAPEUTIC AND TOXIC CONCENTRATION:

The usual therapeutic range of (bound+ unbound) phenytoin is 10-20 µg/ml in plasma for treatment of seizures. Since phenytoin is highly protein bound (90%), it is prone for plasma protein binding displacement. In the upper end of therapeutic range (>15µg/ml) patients experience drowsiness and fatigue. When plasma concentration exceeds 20µg/ml, nystagmus occurs. Above 30 µg/ml ataxia, slurred speech and in-coordination can occur. When plasma levels reach above 40µg/ml mental status changes like decreased mentation, severe confusion, lethargy and coma can occur. Drug induced seizure activity has occurred at concentrations between 50-60 µg/ml(7).

SIDE EFFECTS

Cardiovascular: severe hypotension and arrhythmias can occur when it is infused at the rate of >50mg/min.

Neurological: At therapeutic doses phenytoin may produce nystagmus on lateral gaze, vertical nystagmus, sedation, slurred speech cerebellar ataxia and tremors can occur at toxic doses. Abrupt discontinuation of phenytoin can increase seizure frequency and even progress to status epilepticus. Prolonged use of phenytoin leads to accumulation in the cerebral and cerebellar cortex leading to atrophy of the same.

Haematological: Megaloblastic anaemia, Agranulocytosis and Aplastic anaemia can occur.

Pregnancy: Administration of phenytoin in pregnancy leads to fetal hydantoin syndrome (mild mental retardation, craniofacial abnormalities, cleft lip and palate, as it is a teratogen.

Gastrointestinal: Gingival hypertrophy

Dermatological: Side effects range from itching, rashes and hypertrichosis to life threatening Steven Johnsons and toxic epidermolysis.

Psychiatric: Patients on phenytoin tend to have suicidal thoughts and depression.

Metabolic: Interference with vitamin D metabolism causes severe osteoporosis

DRUG INTERACTION:

Phenytoin is a hepatic enzyme inducer especially the CYP3A4 and CYP2C19 families of the P450 enzyme. This enzyme is responsible for the hepatic degradation of various drugs. Clinical relevance of this property is that concomitant administration of steroids such as dexamethasone and chemotherapeutic drugs can be rendered ineffective.

Antacids interfere with absorption of phenytoin; they significantly reduce the rate and extent of absorption of phenytoin from the gut and therefore put the user at risk of seizures.

Warfarin and Trimethoprim increase phenytoin levels by displacing protein bound drug as well as inhibit the metabolism of phenytoin and thereby increasing the plasma half life.

SODIUM VALPROATE

Valproic acid is a branched chain fatty acid with antiepileptic and mood stabilising properties. Its sodium salt (sodium valproate) is used in clinical practice. Chemical name is sodium 2 propylpentoate (Fig.3). It has been in use since 45 years. It is considered a broad spectrum antiepileptic because it can be used in generalised seizures(absence/tonic-clonic, myoclonic),partial seizures

(simple,complex, secondarily generalised) and also in refractory seizures.

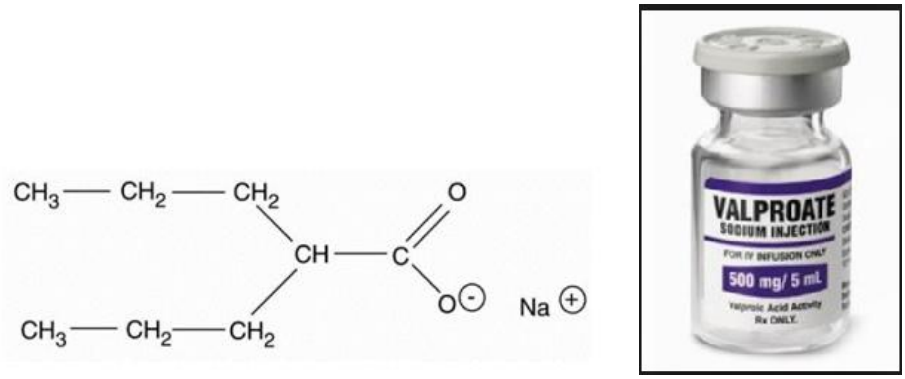


Figure 3: Chemical formula and Intravenous preparation of Sodium Valproate.

MECHANISM OF ACTION:

The mechanism of action of Valproate is yet to be fully understood however most of its antiepileptic activity is from its effect on the inhibitory neurotransmitter GABA. Valproic acid increases the synaptosomal GABA concentrations via activation of the major synthetic enzyme glutamic acid decarboxylase. It also has inhibitory effect on the GABA catabolic enzymes such as succinic semi aldehyde dehydrogenase and GABA transaminase.

Vaproate also reduces the excitatory neurotransmission mediated by gamma-hydroxybutyric acid which is responsible for absence seizures. In addition to its effect on neurotransmitters it also has a direct depressant effect on the neuronal membrane by altering sodium and potassium conductance.

USES:

1. Epilepsy
2. Bipolar disease
3. Migraine

PHARMACOKINETICS:

Peak plasma concentrations after oral doses are achieved in 1-3 hours. Bioavailability is 100% with oral formulations. Volume of distribution ranges from 0.1-0.4L/kg. It is protein bound .Valproate undergoes biotransformation via 5 metabolic pathways, majority of the drug is excreted in free form or as glucuronide conjugates. Clearance ranges from 0.4 to 0.6l/h. It has a low hepatic extraction ratio. Elimination half life ranges from 9-16 hours

THERAPEUTIC RANGE AND TOXICITY:

Therapeutic range is between 50-100µg/ml. At toxic level, CNS depression occurs. It can present with depression, lethargy, encephalopathy, myoclonus and respiratory depression.

DOSE:

1000-2000mg/day in 2 divided doses

SIDE EFFECTS:

Increase in appetite and weight gain, liver failure, pancreatitis, hair loss, edema, ataxia, teratogenicity, tremors, thrombocytopenia and encephalopathy. Suicidal ideation and behaviour is also common.

In pregnant mothers use of Valproate is contraindicated as there is high association with cleft lip and palate

DRUG INTERACTION:

Sodium Valproate is a hepatic enzyme inhibitor thereby causes many drug interactions. When given in combination with phenytoin it increases phenytoin free form as it displaces protein bound drug and inhibits its metabolism.

When administered with vitamin k dependant anticoagulants, the levels of anticoagulants may increase therefore close monitoring of INR is recommended.

Carbapenem antibiotics, antimalarial agents such as Mefloquin and chloroquin may decrease Valproate levels and lower seizure threshold.

Major Anaesthetic Concerns in Supratentorial Craniotomies:

Preoperative assessment:

In addition to routine pre-anaesthetic evaluation, attention to tumor location, size and type , presence of peritumoural edema, signs of raised ICP are given special consideration while evaluating patients with supratentorial tumors.

History usually reveals one sided headache, blurring of vision, nausea and vomiting. History of loss of power in a particular limb or side gives an idea about the location of tumor. History of seizures type, duration and anti seizure medication that the patient is on are noted.

Examination includes assessment of sensorium along with a thorough assessment of central nervous system for motor and sensory deficits.

Investigations: routine preoperative blood tests such as hemoglobin, creatinine, blood borne virus screen, electrocardiogram, chest X-ray as well as special imaging such as CT and MRI for tumor size site, type and midline shift.

Preoperative preparation:

Patients are fasted overnight. Premedication is generally avoided if patients have midline shift >5mm suggesting significant cerebral edema, as over sedated patients tend to retain carbon dioxide further increasing the intracranial pressure. Adequate blood should be cross matched and typed ready for transfusion as required intraoperatively.

Intraoperative management:

In addition to standard monitors recommended by ASA standards, special monitors placed in supratentorial craniotomies include an invasive arterial line, central venous line and neuromonitoring. Neuromonitoring includes central sulcus mapping and motor/sensory evoked potential monitoring.

The major concern in neuroanaesthesia is to maintain optimal cerebral perfusion pressure (mean arterial pressure-intracranial pressure). Cerebral perfusion pressure is thus maintained by manipulating the ICP and mean arterial pressure. Close hemodynamic monitoring warrants placement of an invasive arterial line. Invasive blood pressure monitoring gives us beat-to-beat variation in blood pressure. Risk of bleeding and venous air embolism, need to rapidly infuse vasopressors drugs, indicate the placement of a central venous catheter placement. The requirement for special monitoring is decided on a case-to-case basis: neuromuscular monitoring should be used if muscle relaxants are given during the surgery especially if used as an infusion. Electroencephalography (EEG) based monitor such as BIS(Figure 4)or entropy not only provide information about the depth of anaesthesia, it also helps us titrate anaesthetics in patients with increased intra cranial pressure. It gives us information about the occurrence of intraoperative seizures and to induce electrical silence in presence of cerebral ischemia. Monitoring of evoked potentials is helpful in observing intactness of specific central nervous system pathways during surgical manipulation.

Anaesthetic Management:

Carefully titrated induction and measures to attenuate larygoscopic pressor response is of utmost importance in order to prevent further increase in intracranial pressure and decrease in cerebral perfusion.

Anaesthetic aims during maintenance of anesthesia during supratentorial surgery are:

1. Control of intracranial pressure via control of cerebral blood flow and cerebral metabolic rate (chemical brain retractor concept).

Components of this concept encompass the following:

- Maintaining the blood Osmolality to mild hyperosmolar by giving 20% mannitol or 3% Saline and by giving NaCl based solution.

- Intravenous anaesthetic agent (Propofol) to reduce the cerebral blood volume by vasoconstriction.

- Mild hyperventilation – to reduce the cerebral blood flow by causing vasoconstriction.
- Mild controlled hypertension: Maintaining the mean arterial blood pressure of 100 mm Hg to maintain the cerebral perfusion pressure.
- By maintaining normovolemia
- By maintaining normoxemia
- By positioning the patient slightly in Head-up with no jugular compression

- By avoiding positive end-expiratory pressure
- By keeping the patient in deeper plane and avoid coughing and bucking on the ventilator by using adequate muscle relaxant
- By avoiding excessive brain retraction
- By draining the CSF through Lumbar drainage

2. Neuroprotection through maintenance of optimal intracranial environment: maintain a good match between cerebral substrate demand and supply. Although some anaesthesiologists use moderate hypothermia (35˚ degrees Celsius) to provide Neuroprotection, clinical studies have not demonstrated any beneficial effect of the same in neurosurgical patients.

Awakening from neurosurgery mandates maintenance of stable arterial blood pressure (and thus, cerebral blood flow and intracranial pressure), stable oxygenation, carbon dioxide tension and normothermia. Careful attention is paid so as to avoid coughing and bucking during extubation. Extubation is associated with significant hemodynamic fluctuations. These fluctuations may not be critical in usual subjects, however in neurosurgical patients careful and smooth extubation goes a long way in postoperative outcomes. Coughing, bucking and hypertension lead to rupture of incompletely cauterized blood vessels and thus cause postoperative hematomas and seizures.

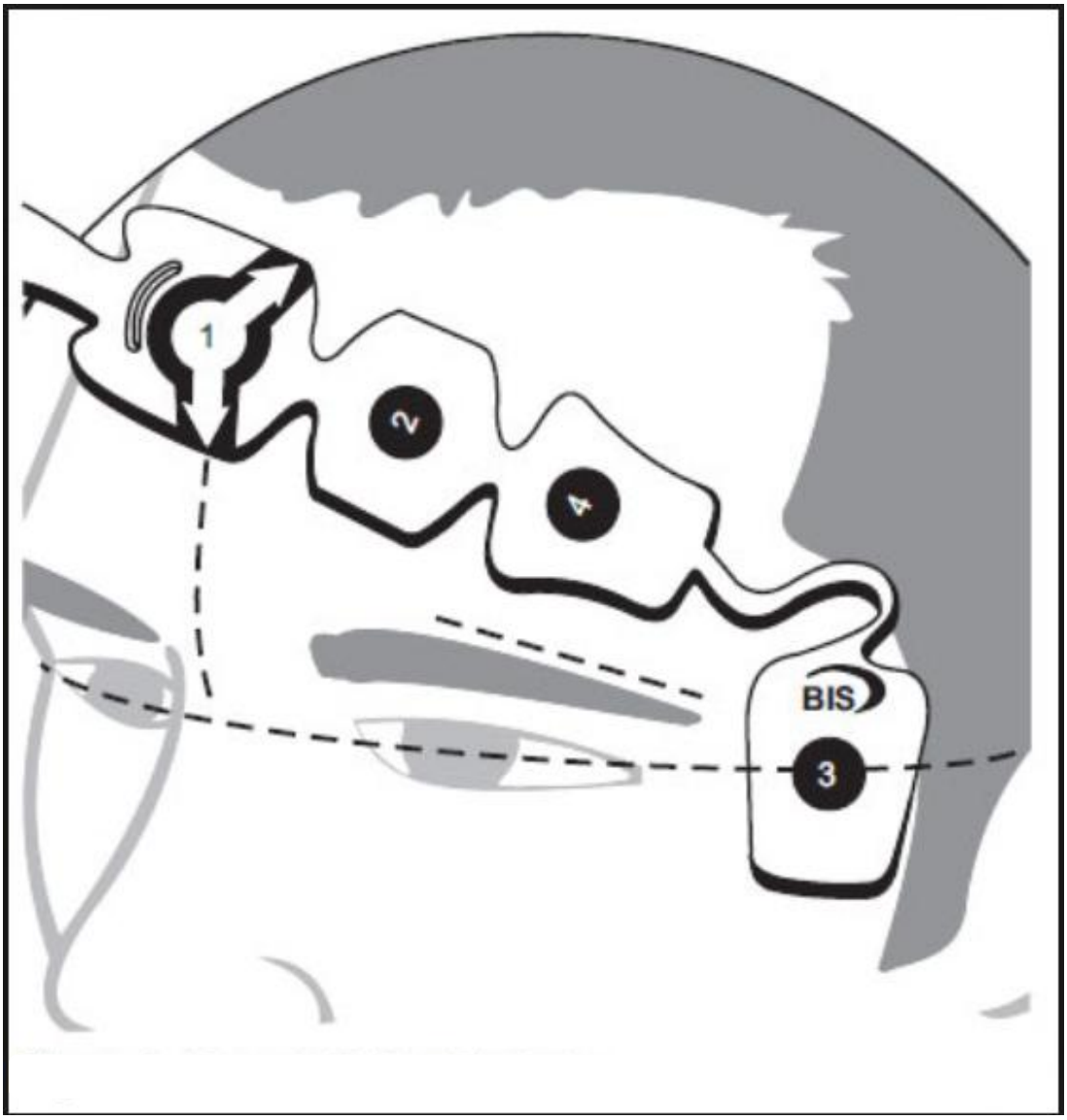


Figure 4: BIS electrode placement to monitor depth of anaesthesia

Recovery from anesthesia after supratentorial craniotomy

A conscious individual is awake and aware of surroundings and identity. Most often consciousness is assessed by the Glasgow coma score. Initially the Glasgow coma score was used in patients with head injury but it is now commonly used to assess consciousness no matter what the etiology. It includes verbal response, motor response and visual response. The minimum score is 3 and maximum is 15. A score <8 is considered coma. Anesthesia is a way to make a patient unconscious for the duration of the surgery so that he is unaware of his surrounding and unable to react to painful stimuli. This state of unconsciousness is reversible. The duration of time necessary to awaken after anesthesia to a state of normalcy is termed recovery time. There are many factors which affect this time duration, they may be patient related, anesthetic factors and drugs, duration of surgery and other organic conditions.

1. Surgical factors include:

    Duration of surgery, use of excessive brain retraction, type and location of brain tumour, presence of residual tumour, tumor bed haematoma.

2. Patient factors:

    extremes of age, genetic variations, renal/hepatic disease

3. Drug related:

    residual effects of opioids, benzodiazepines, long acting muscle relaxants.

4. Anaesthesia related:

residual anesthetic effect, opioid overdose, residual relaxant effect , Hypoxia, hypercarbia, acidosis, hypothermia

5. Metabolic causes:

Hyponatremia, Hypernatremia, Hypoglycemia, Hyperglycemia Hypothermia, Hypothyroidism, Central anti cholinergic syndrome.

6. Central nervous system causes:

Central hypoxia, Cerebral edema, Seizures, Ischemia, Hemorrhage, Local anesthetic toxicity

7. Respiratory causes:

Sepsis/ARDS, Respiratory failure, Depression Central respiratory drive

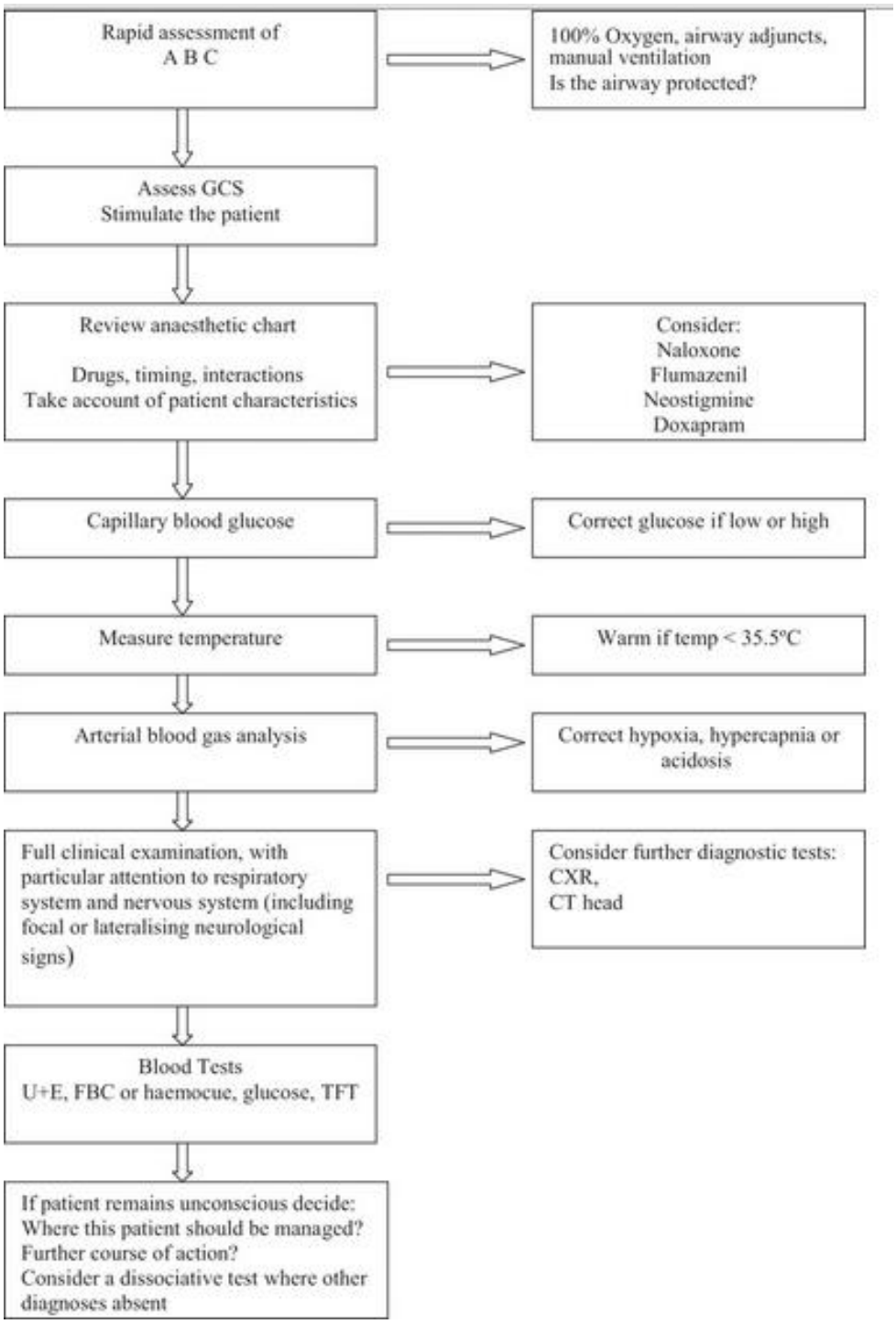


Figure 5: A Flowchart showing the management of Delayed awakening after anesthesia

Seizure prophylaxis –the current stand

Seizures are one of the more serious complications of brain tumour surgery as they can delay recovery and even cause death. Seizures occur in 20-40% of patients with brain tumours(8). Frontal and parietal tumours and those that are slow growing are more likely to cause seizures.

Several studies have been done to look at the incidence of seizures with and without prophylaxis with conflicting results. Some studies have shown a decrease in plasma levels of anticonvulsant at the end of craniotomies, suggesting that a bolus administration of drug intraoperatively can overcome this drop in levels. The drop in anticonvulsant levels being attributed to blood loss and blood transfusion during surgery, haemodilution with administration of IV fluids, long duration of surgery and probably drug interaction with dexamethasone(9).

Plasma phenytoin levels and incidence of seizures following craniotomy for supratentorial brain tumors by **Phunsawat et al** studied 20 patients, plasma phenytoin levels dropped by 29.6% in 14 patients and increased by 52% in 6 patients. 3 out of 20 patients had post craniotomy seizures even with therapeutic phenytoin levels. The cause for seizures being postoperative bleed and cerebral edema(10).

Additional phenytoin is frequently needed in patients undergoing craniotomy for supratentorial tumour **Umamaheshwara Rao et al** -25 patients were studied 44% had sub therapeutic phenytoin level, 2 patients had post craniotomy seizures even with therapeutic plasma levels(11).

Changes in plasma phenytoin level following craniotomy **J S Yeh et al** studied 28 patients. In this study less than 50% has preoperative therapeutic levels, in most (89%) patients there was a decrease in phenytoin levels by 26%. None of the patients had seizures post operatively(9).

The latest guideline on seizure prophylaxis published by the **American academy of neurology,2002** recommends the avoidance of the use of anticonvulsants prophylactically in patients with brain tumours as they are not beneficial in preventing the first episode of seizure(2).

Anticonvulsant prophylaxis for brain tumor surgery : determining the current best evidence **Eli et al** looked into 2 meta analyses and recommended that their use does not improve seizure control in these patients and hence should be avoided.(12)

Despite these guidelines that discourage the use of anticonvulsant they continue to be administered to patients with brain tumors by neurosurgical practitioners, so also in our institution. The aim is to attain therapeutic levels and steady state plasma concentration preoperatively (phenytoin- 10-20mcg/ml and Valproate- 40-100mg/ml).

Effect of anticonvulsants on hemodynamics depth and recovery

The older generations of anticonvulsants were known for their sedative effects, however the currently used anticonvulsants such as Valproate and phenytoin also have some sedative effect. A study done in Turkey by **Isil gogcegoz et al** showed the reduced requirement of Propofol in patients receiving Valproate who were undergoing ECT .The dose required to reach BIS of 60 was lesser in those patients on Sodium Valproate(13).

Few case reports of hemodynamic disturbances with the administration of bolus doses of phenytoin more so than Valproate. Cardiac arrest after rapid intravenous administration of phenytoin have also been reported(14).

Phenytoin and Valproate have been implicated in cognitive dysfunction. Antiepileptics are administered to patients with brain tumors and cognitive dysfunction commonly attributed to the tumor and cerebral edema, however studies have shown that phenytoin and Valproate may be responsible for cognitive dysfunction(3). This study aims at recognizing the possibility that administration of large doses of antiepileptics themselves may be responsible for early postoperative cognitive dysfunction and delay in recovery time.

MATERIALS AND METHODS

Patient Selection and Methodology

Settings

This study was carried out in the three Neurosurgery operating theatres and Neurosurgery Intensive Care Unit of Christian Medical College and Hospital, Vellore.

Inclusion Criteria

1. Supratentorial brain tumours
2. Age 18-60 yrs
3. ASA grade 1,2 &3
4. Patients on single AED for more than 1 week.

Exclusion Criteria

1.Pregnancy

2.Severe LV dysfunction

3.Kidney disease

4.Liver disease

5.H/o seizures on AED within a week

6.Surgery lasting for > 5 hours.

7.Blood loss > 30% of blood volume will be excluded.

8.Deep seated tumour which needs brain retraction

9. Preoperative GCS<15

Sample Size

Sample size: Assuming that the mean recovery time for group 1 will be 15 mins (SD=5) and for group 2 will be 25 mins (SD=6), the minimum required number to test the significant difference between the two groups is 9 samples each. So the sample size for this study is decided to be 40

Since there are 4 strata (phenytoin regular dose/Valproate regular dose/ phenytoin additional dose/Valproate additional dose) each group will have 10 sample and hence a total sample size of 40

The calculation is done by using nmaster 2.0 software.

Two Means - Hypothesis testing for two means

Standard deviation in group I	5
Standard deviation in group II	6
Mean difference	10
Effect size	1.818182
Alpha error (%)	1
Power (1- beta) %	90
1 or 2 sided	2
Required sample size per group	9

Methodology

Patients who meet the inclusion criteria for the study will receive standardized anaesthesia as follows:

1.**Premedication:**

No sedative premedication was given to all patients undergoing supratentorial craniotomy. Routine dose of anticonvulsant dexamethasone and ranitidine was continued as per schedule.

2. Intraoperative period

After wheeling the patient in operating room, standard monitors like ECG, SpO_2, NIBP, were connected. 18 or16 G peripheral line, 20 G arterial line was started. First blood sample was taken for checking the anticonvulsant level. After adequate preoxygenation with 6 L/min of 100% oxygen, patients were induced with 1-2 µg/kg of fentanyl, 1.5 -2 mg/kg of propofol and paralysed with 0.1 mg/kg of vecuronium.

After 3 min of ventilation and after achieving 1 MAC concentration of isoflurane, patient's trachea was intubated. After securing airway, anaesthesia was maintained using 0.8-1 MAC Isoflurane in air and oxygen (40%) mixture. FGF were reduced to 2L/ min for 20 min. Then the FGF were reduced to 750 ml- 1L/min. Temperature probe, BIS monitor and neuromuscular monitor were connected after intubation. Muscle relaxation was maintained with infusion of Vecuronium at 1 ug/kg/min, and its response was monitored using Train Of Four (TOF) Ratio in neuromuscular monitoring device.

Additional dose of 0.5 µg/kg of fentanyl and 0.5mg/kg of propofol were given intravenously along with local anaesthetic infiltration at pin site at the time of insertion Mayfield head clamp. 20-30 ml of 0.25% Bupivacaine with adrenaline (5 µg/ml) was given for scalp flap infiltration.

Anaesthesia and muscle relaxation were monitored and maintained constant as described earlier. Any additional significant sympathetic response producing rise in heart rate and BP > 20% from the baseline was treated with 0.5 mg/kg of propofol and if required 0.5 µg/kg of fentanyl.

For patients who were supposed to receive an additional dose of anticonvulsant, it was given during the start of bone flap removal. The drug was administered over a period of 15-20 mins during which the changes in haemodynamics and BIS were noted down. Intraoperatively, fluids (crystalloid,colloid,blood) were be given according to the PPV(pulse pressure variation) changes. PPV was maintained below 13.

While achieving haemostasis, BP was brought to pre-induction level with small doses of vasopressors (ephedrine or phenylephrine) and IVF. During the dural closure 0.5µg/kg of fentanyl was given along with 15 mg/kg of paracetamol. Another 0.5 µg/kg of fentanyl , given if needed during the scalp flap closure. 0.1 mg/kg of ondansetron was given 20 min prior to end of surgery. Concentration of isoflurane was reduced at the time of skin closure to keep MAC of 0.6-0.7. Isoflurane was cut off while applying skin dressing but FGF were not increased. Xylocard 1-1.5 mg /kg was given while applying the

skin dressing to prevent coughing while removing the May field head clamp. FGF were then increased to 6-8L/min only after the removal of pin.

3. Reversal and recovery:

Patients were reversed using neostigmine (50 µg/kg) and glycopyrroate (10 ug/kg). The patient was not stimulated (call their names, or suction) and the respiratory rate was not changed to bring the CO2 up till the MAC came down to 0.3. Time taken from stopping the isoflurane to extubation was recorded as Extubation time. Time taken to open their eyes was noted.

4.Postoperative care and follow up:

After extubation, Second blood sample was taken for checking the plasma level. Recovery was assessed based on time taken to open eyes, time taken to obey commands and time to orientation to place and person

RESULTS

In this study a total of 36 patients were studied, 19 patients received phenytoin and 17 patients received sodium valproate. Out of 19 patients who received Phenytoin, 12 patients received the regular dose (no bolus) and 7 patients received additional or bolus dose of phenytoin during craniotomy. Out of 17 patients who received sodium valproate, 10 patients received additional valproate and 7 patients received only the regular dose during surgery. Patients who received the regular dose are marked as **regular** group and patients who received additional dose are marked as **additional** group as shown in Table 2.

Table 2: No of patients who received the regular dose Vs additional dose:

Group (Total No of patients)	Regular Group	Additional Group
Phenytoin (19)	12	7
Sodium valproate (17)	7	10

Demography:

Age and Body weight:

Patients between 18 and 70 years of age were recruited in this study. The mean age of patients who received regular phenytoin was 45years and for additional phenytoin was 43 years. The mean age of patients who received regular sodium valproate was 45 years and for the additional dose was 44 years . Since the age of a patient has significant impact on requirement of anaesthesia as well as the recovery, we wanted to see whether the age distribution is uniform even if we divide the age group further into less than 45 and more than 45 yrs. We did not see any significant difference in age distribution between the groups.

Table 3: Age distribution between the two groups.

Groups	Regular Group		Additional Group	
	< 45 yrs	> 45 years	< 45 yrs	> 45 yrs
Phenytoin (No of pts)	7	5	4	3
Sodium valproate (No of pts)	3	4	5	5

There was no significant difference in distribution of age between the groups as shown in Table 3.

The mean body weight was 59.3 kilogram for regular group and 62kilogram for additional group. There was no difference in body weight between the two groups.

Gender:

Out of 36 patients, there were 12 males and 7 females who received regular dose. There were 7 males and 10 females who received the additional dose (Figure 6a). Over all, there were more males in patients who received phenytoin and more females in patients who received sodium valproate (Figure 6b).

Figure 6a: Sex distribution among two groups.

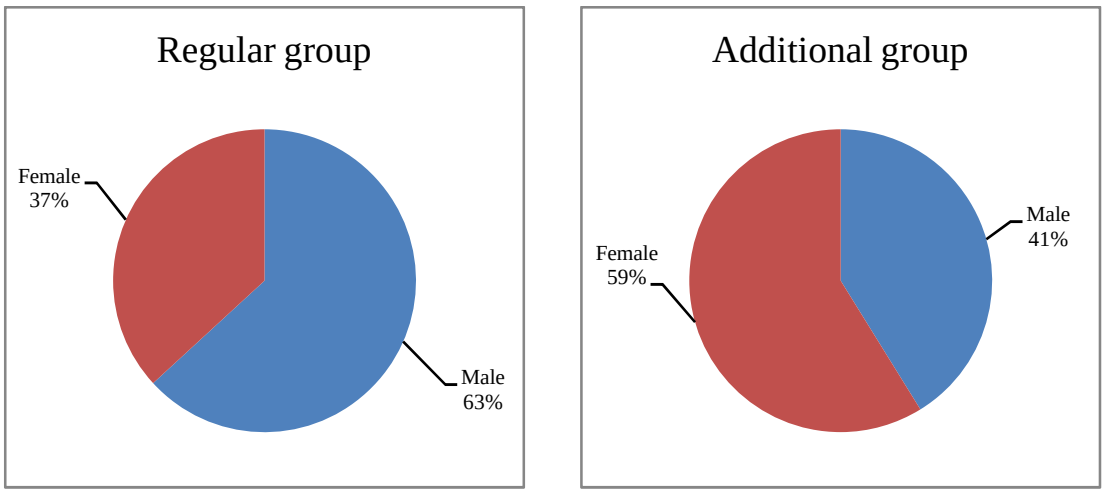
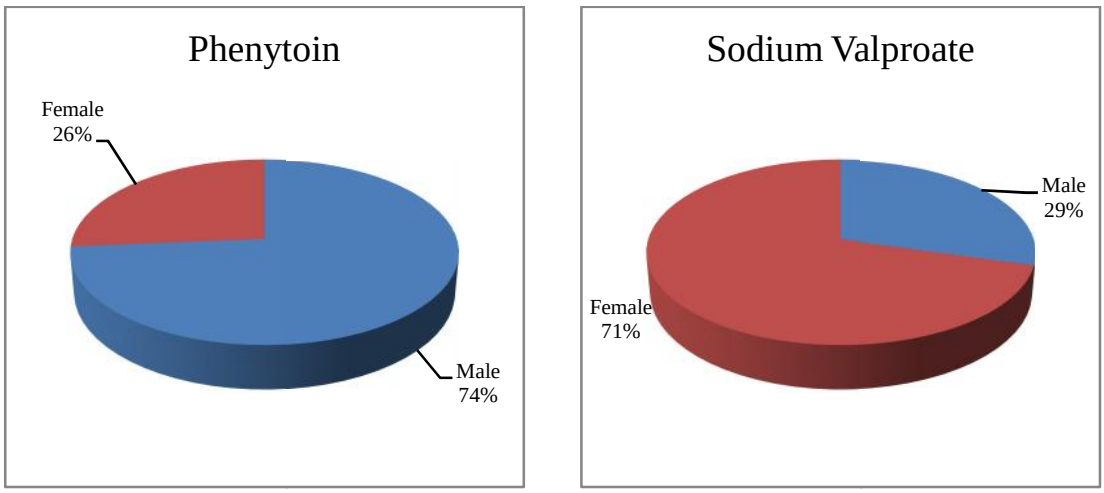


Figure 6b: Sex distribution among patients who received phenytoin and sodium valproate.



In this study, our primary outcome was to assess the recovery time in patients receiving additional Vs regular dose. The tumour type, location, presence of preoperative seizures all can affect the recovery from anaesthesia. So we wanted to compare the distribution of these factors between the two groups.

Tumour Pathology:

There was no significant difference in distribution of tumour pathology between the two groups. (Figure 7a:7b). Most patients in both groups had meningioma; it is one of the most common benign intracranial lesions. Following meningioma, glioma was the second common tumour type seen in both the groups.

Figure 7a: Distribution of tumour pathology in the Regular group

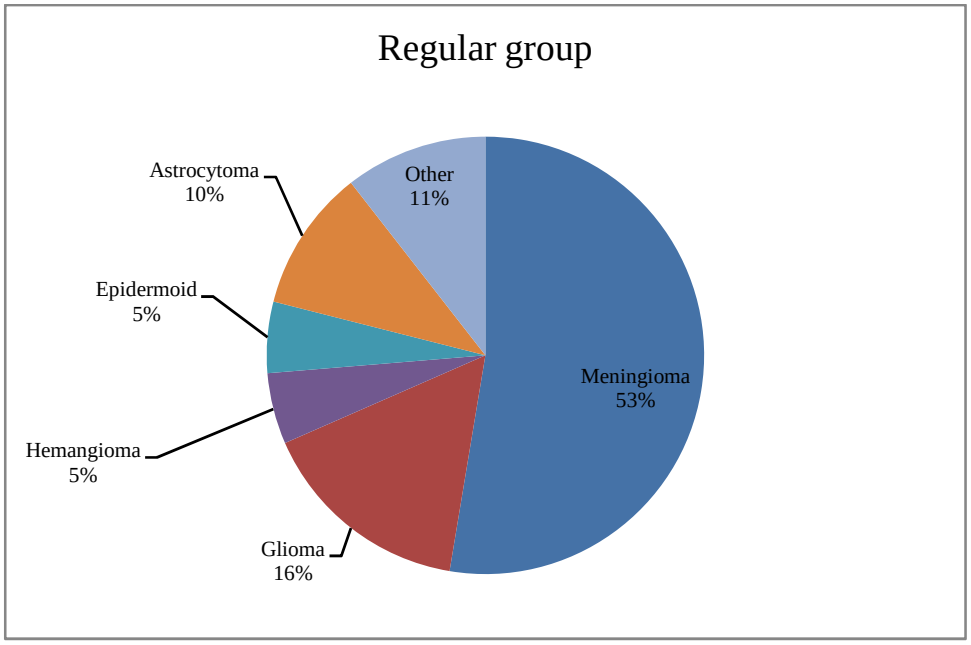
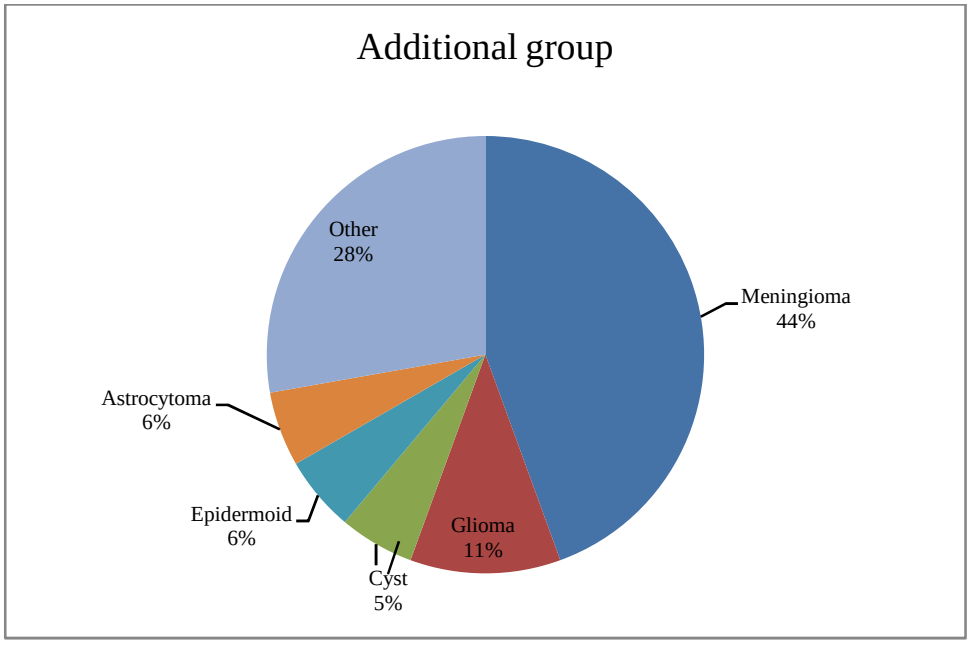


Figure 7b: Distribution of tumour pathology in the Additional group.



Tumour location:

Tumour location also has a significant impact on recovery from anaesthesia. Tumours located on certain areas of brain eg. the frontal cortex, can cause delayed awakening. Most patients in both the groups had frontal tumours, followed by parietal tumours. There was no significant difference in tumour location between the two groups. Figure 8a: 8b showing the distribution of tumour location between the two groups.

Figure 8a: Tumour location in Regular Group.

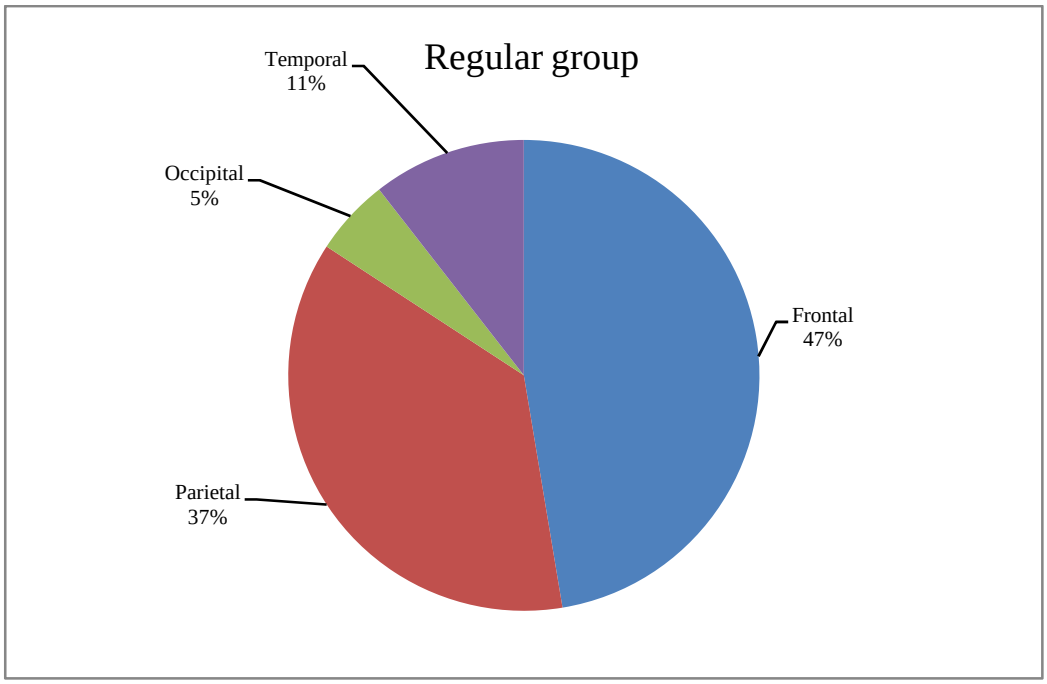
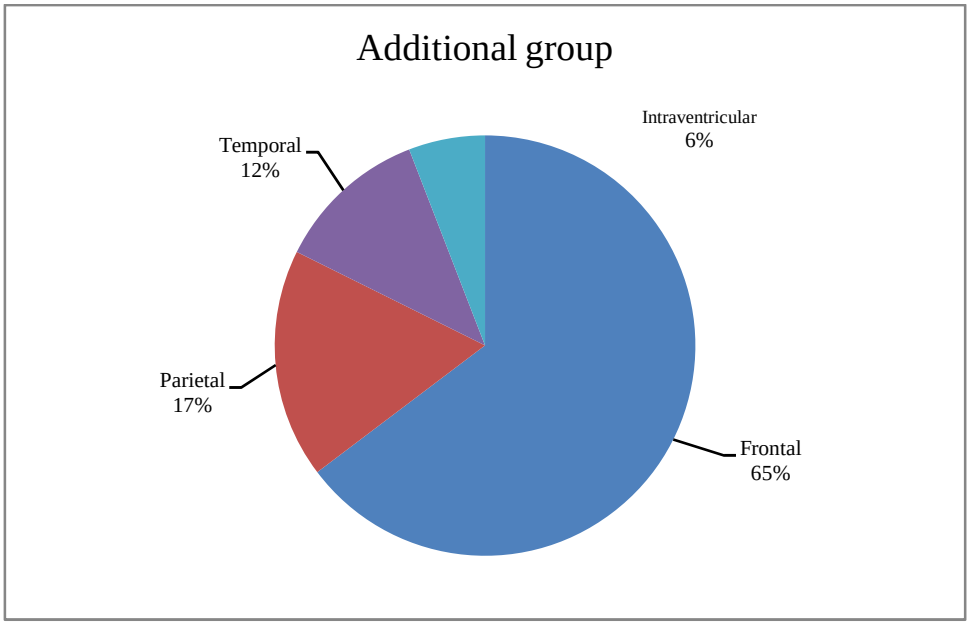


Figure 8b: Tumour location in Additional Group.



Presence of Preoperative seizures:

Presence of preoperative seizures is one of the risk factor for development of intra and post operative seizures which can delay the awakening from anaesthesia.

Table 4: No of patients who presented with preoperative seizures in both groups:

Group	Regular Group (19)		Additional Group (17)	
	Seizures Yes	Seizures No	Seizures Yes	Seizures No
Phenytoin	8 (67%)	4 (33%)	3 (43%)	4 (57%)
Sodium Valproate	2 (29%)	5 (71%)	4 (40%)	6 (60%)

In the regular group, 10/19 patients had presented with seizures. In the additional group, 7/17 patients had presented with seizure for which they were on anticonvulsants. There is no significant difference found between the two groups.

No of patients with medical co-morbidities between the two groups:

Presence of medical co-morbidities can also affect the recovery of anaesthesia. Most patients in both the Groups were ASA 1. In regular group, 8/19 patients were ASA 2 and in the Additional Group 7/17 patients were ASA 2. There was no significant difference found between the two groups as shown in Table 5.

Table 5: Distribution of comorbidities between the two groups

Co-morbidities	Regular Group (19)	Additional Group (17)
No co-morbidities	11	10
Diabetes Mellitus	2	1
Hypertension	6	5
Ischemic Heart Disease	0	1

Duration of Anaesthesia:

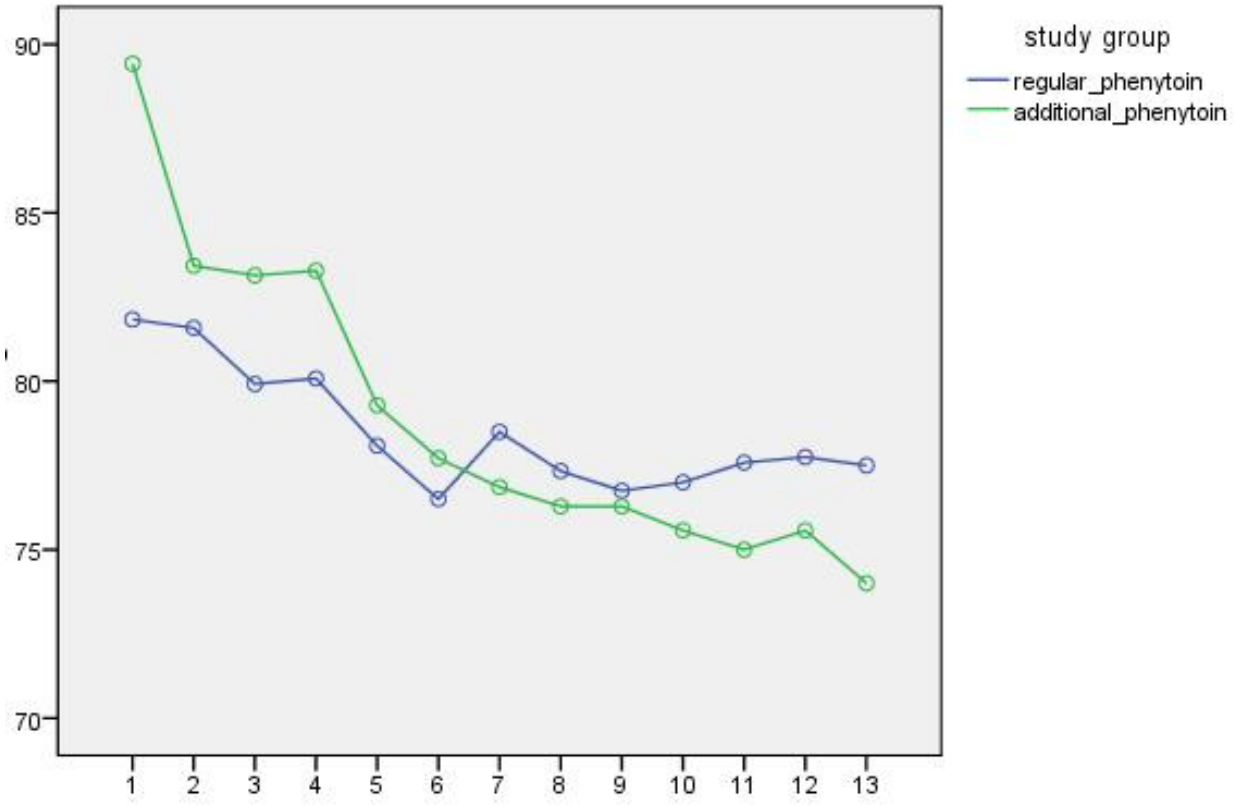
The mean duration of anaesthesia was 285 min in Regular group and it was 279 min for the additional group. There was no significant difference in duration of anesthesia between the two groups.

Effect of administration of anticonvulsants on heart rate:

Since the Phenytoin and sodium valproate have variable effect on the heart rate, we wanted to study the effects of anticonvulsant on heart rate separately for phenytoin and sodium valproate. Heart rate was noted at 5 min prior to anti convulsant administration and noted as baseline. From the time of drug administration to next 60 mins the heart rate changes were noted at every 5 mins. A total of 13 time periods in which, the heart rate changes were studied.

In the additional Phenytoin group, there was a drop in heart rate noted from 20 min of drug administration and it continued till the end of monitoring period, when compared to regular group. Though the drop was clinically significant, it was not statistically significant(p value 0.302) because of small sample size.

Figure 9a: Dot plot comparing the effect of Phenytoin on Heart rate at various time points between the two groups.

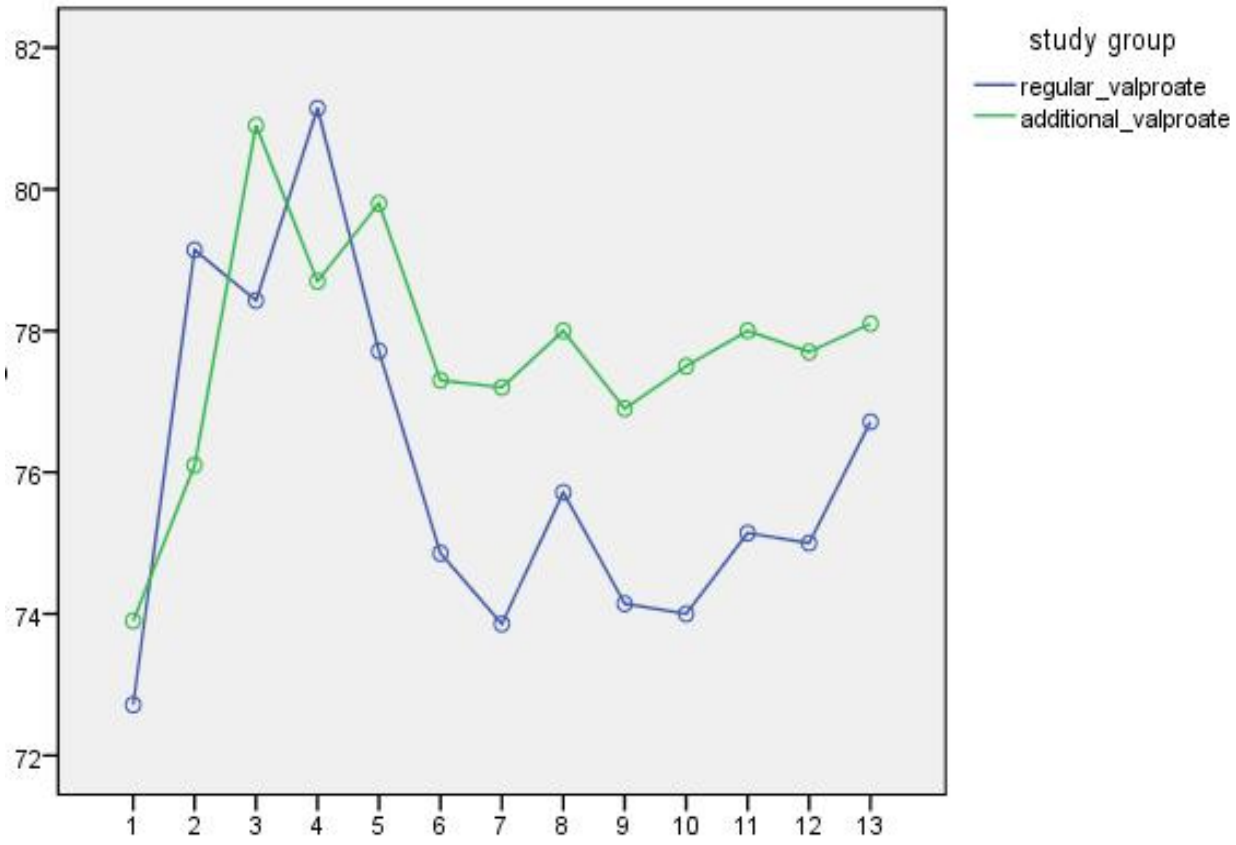


X- axis : Various time points of HR measurement (1=baseline 2=5min,3=10min,4=15min...13=1hour)

Y- axis: Heart rate in beats /min , (HR- Heart Rate).

On the other hand, in the Valproate group, the heart rate was noted to be in higher range in additional group compared to regular group, however the difference is not statistically significant (p value 0.602)

Figure 9b : Dot plot comparing the effect of Valproate on Heart rate at various time points between the two groups.



X- axis: Various time points of HR measurement (Time 1=baseline, 2=at 5min, 3=10min….13=1hour)

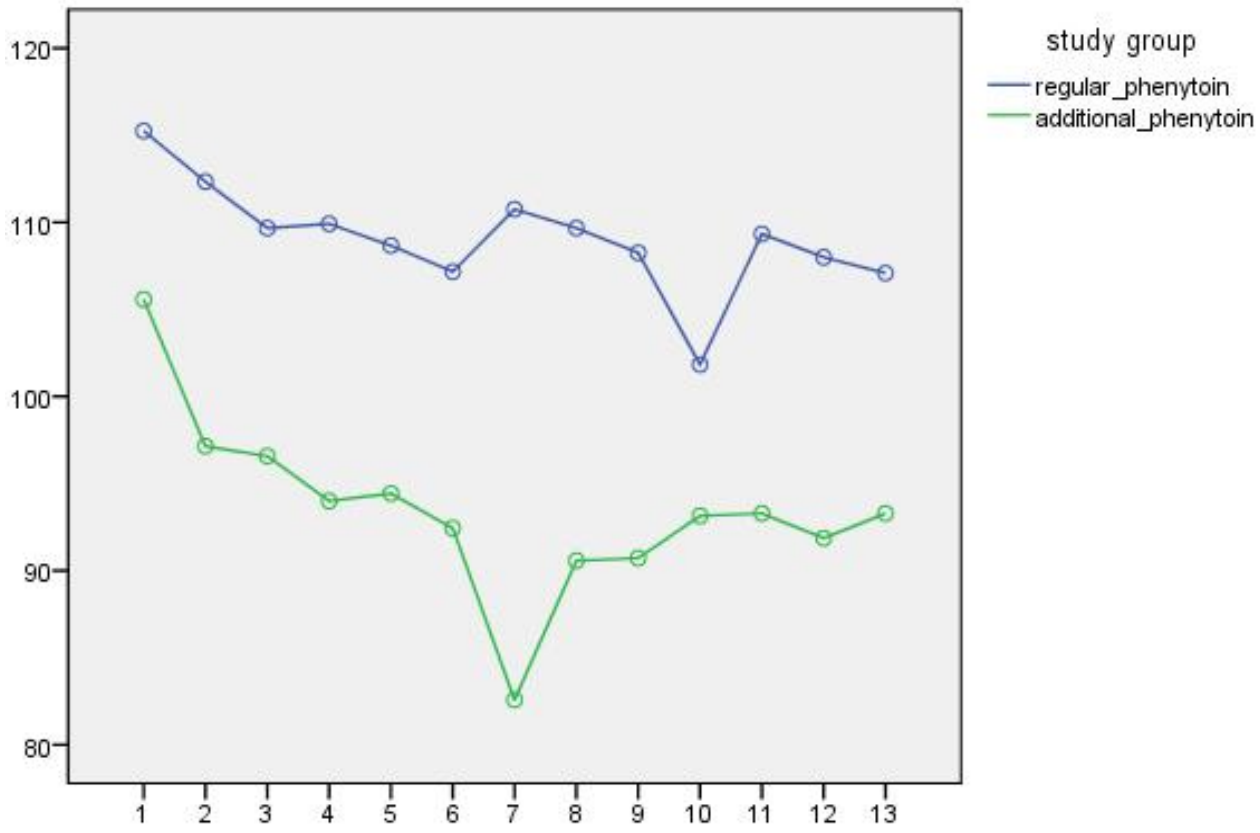
Y- axis: Heart rate in beats/min (HR- heart rate)

Effect of anticonvulsants on systolic blood pressure (SBP):

Since the Phenytoin and sodium valproate have variable effect on blood pressure, changes in blood pressure was plotted separately for phenytoin and sodium valproate. Similar to heart rate recordings, the SBP changes were studied at 13 time periods for both the drugs and compared.

In the Phenytoin group, the trends of systolic blood pressure were lower in additional group compared to regular group as shown in the figure (10a). Though it looked clinically significant, it was not statistically significant. (p value 0.559)

Figure 10a : Dot plot comparing the effect of phenytoin on systolic blood pressure between the two groups.

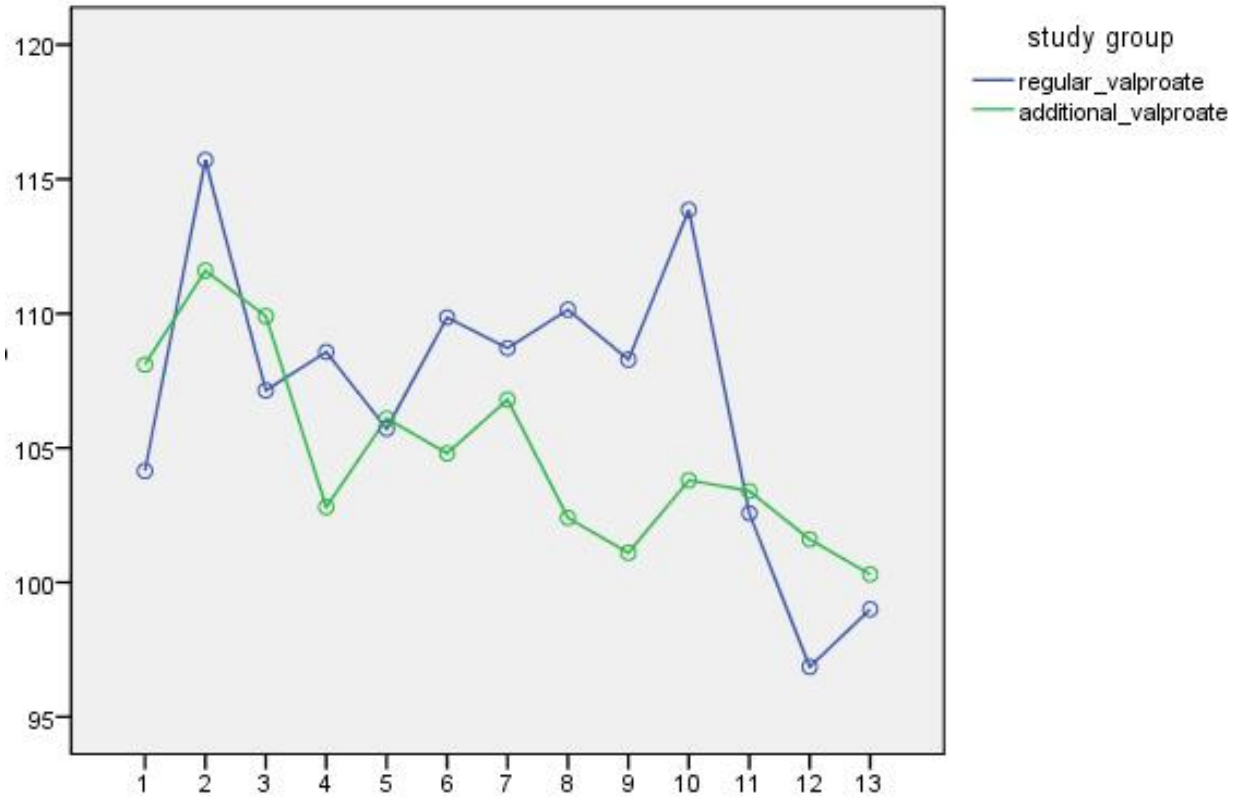


X- axis: Various time of SBP measurement (1=baseline,2=at 5min.3=10min….13=1hour)

Y-axis: Systolic blood pressure in mm Hg (SBP-Systolic blood pressure)

Even in the Valproate group, the trends in systolic blood pressure were lower in the additional group compared to regular group however this was not statistically significant.(p value 0.521).

Figure 10b : Dot plot comparing the effect of valproate on systolic blood pressure between the two groups.



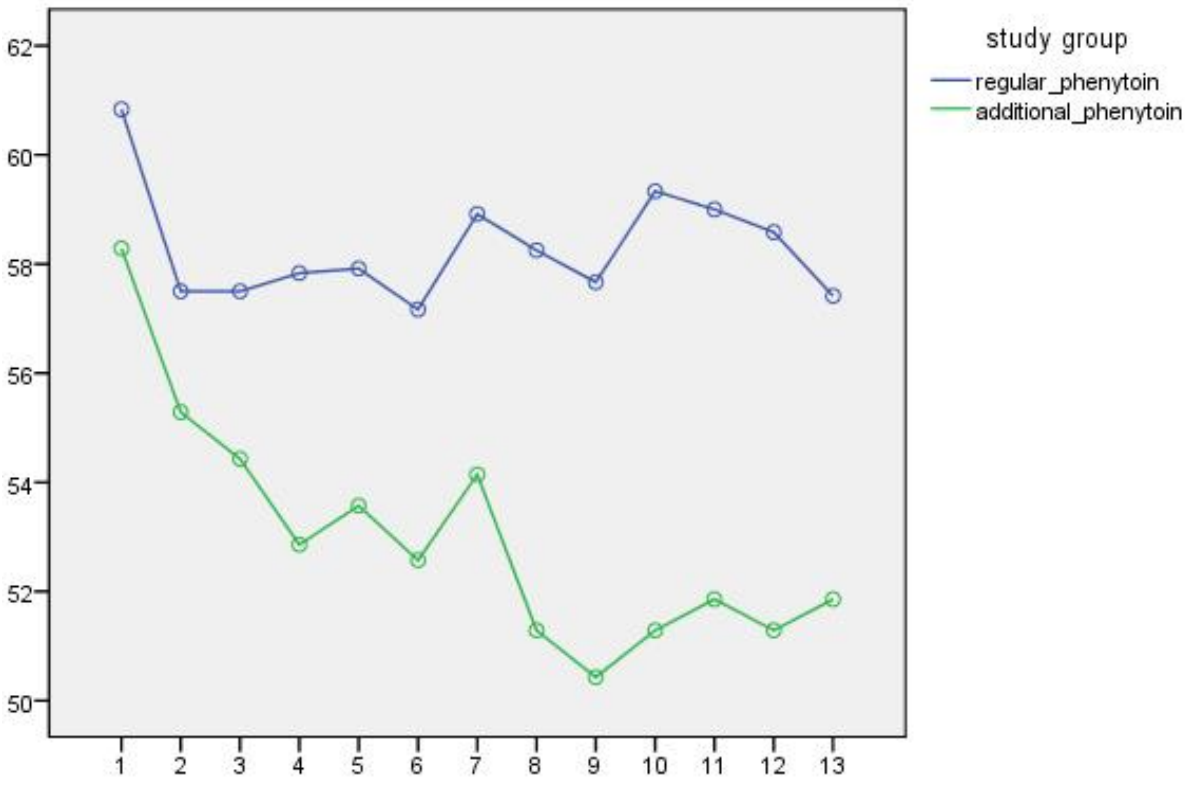
X -axis : Various time points of SBP measurement (1=baseline,2=at 5min,3=10min….13=1hour)

Y-axis: Systolic blood pressure in mm Hg (SBP- Systolic blood pressure)

Effect of anticonvulsants on diastolic blood pressure (DBP).

The diastolic blood pressure was lower in patients who received additional phenytoin compared to regular group as shown in Figure 11a . (p value 0.556).

Figure 11a : Dot plot comparing the effect of phenytoin on diastolic blood pressure between the two groups.

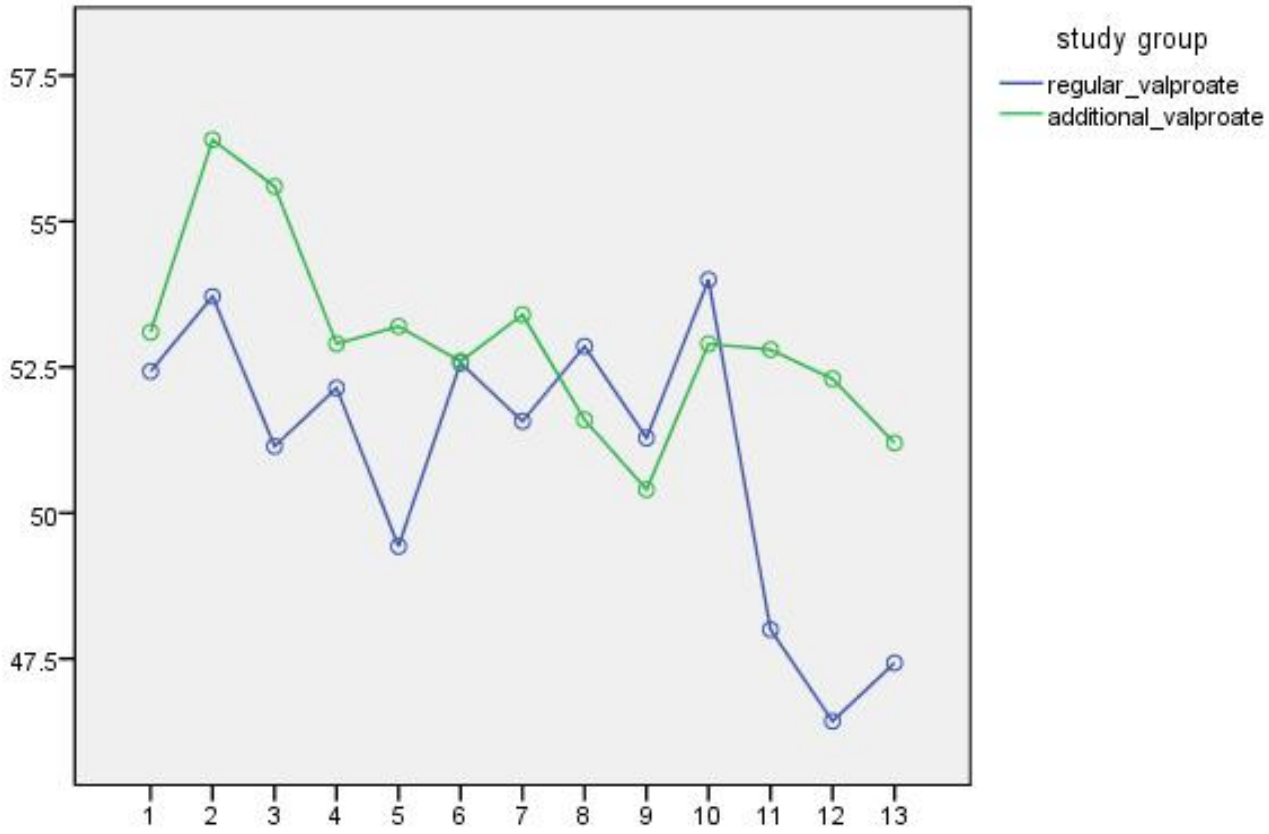


X - axis: Various time period of DBP measurement (1=baseline, 2=at 5min.3=10min….13=1hour,

Y- axis: Diastolic blood pressure in mm Hg (DBP)

In patients who received Valproate, the DBP was almost similar in both groups at most part of the study time as shown in Figure11b . (p value 0.653)

Figure 11b : Dot plot comparing the effect of phenytoin on diastolic blood pressure between the two groups.



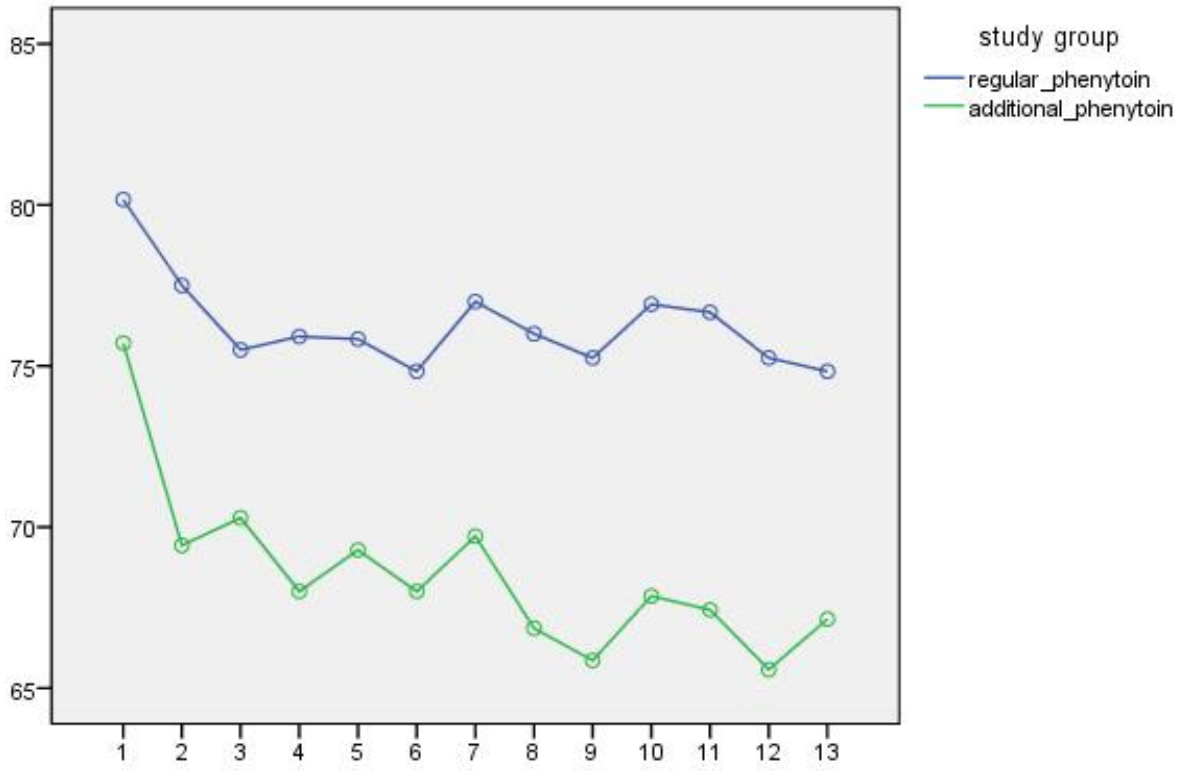
X- axis: The various time period of DBP measurement(1=baseline,2=at 5min.3=10min….13=1hour)

Y- axis: Diastolic blood pressure in mm Hg

Effect of anticonvulsants on Mean blood pressure (MBP):

In the phenytoin group, the mean blood pressures were lower in the additional group when compared to the regular group which was statistically not significant (p value 0.88)

Figure 12a : Dot plot comparing the effect of phenytoin on mean blood pressure between the two groups.

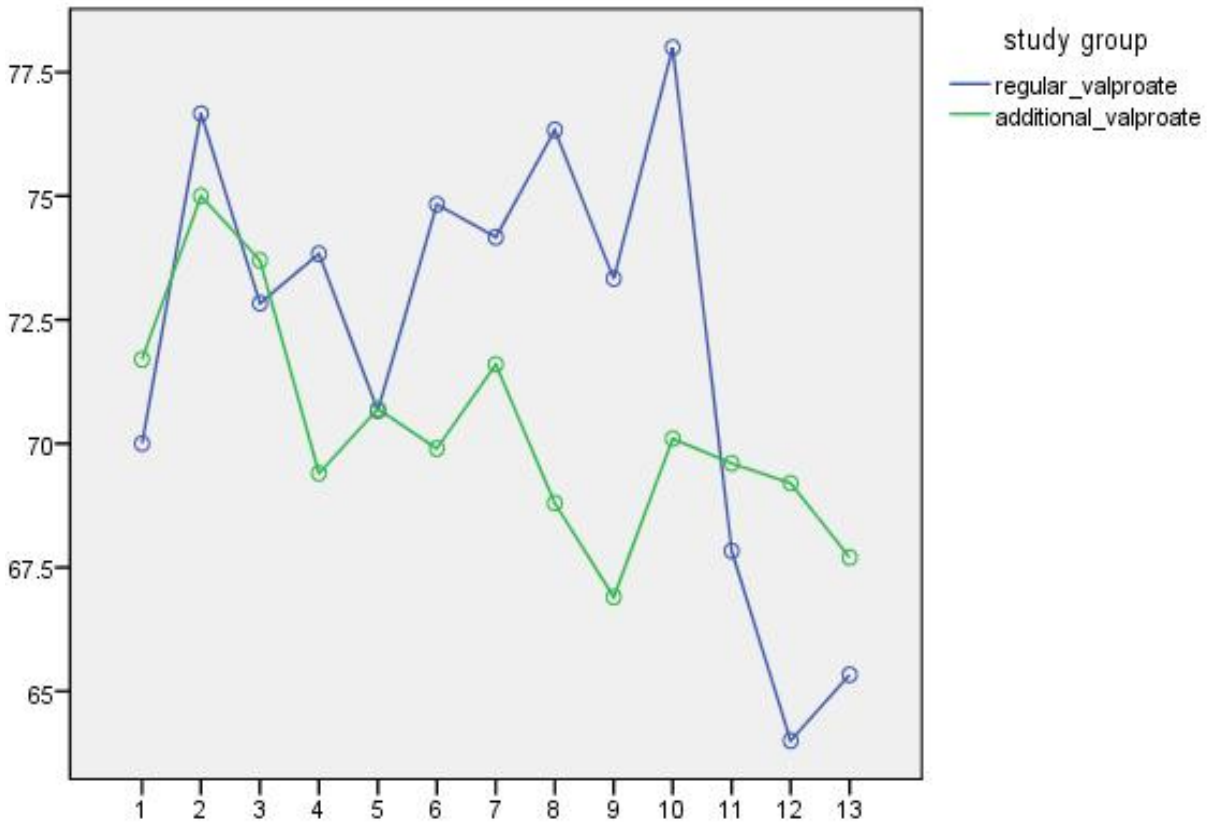


X - axis: Various time period of MBP measurement (1=baseline, 2=at 5min.3=10min….13=1hour,

Y- axis: Mean blood pressure in mm Hg (MBP)

In the Valproate group the mean blood pressure was also lower in the additional group when compared to the regular group across most time points.

Figure 12b : Dot plot comparing the effect of valproate on mean blood pressure between the two groups.



X - axis: Various time period of MBP measurement (1=baseline, 2=at 5min.3=10min….13=1hour,

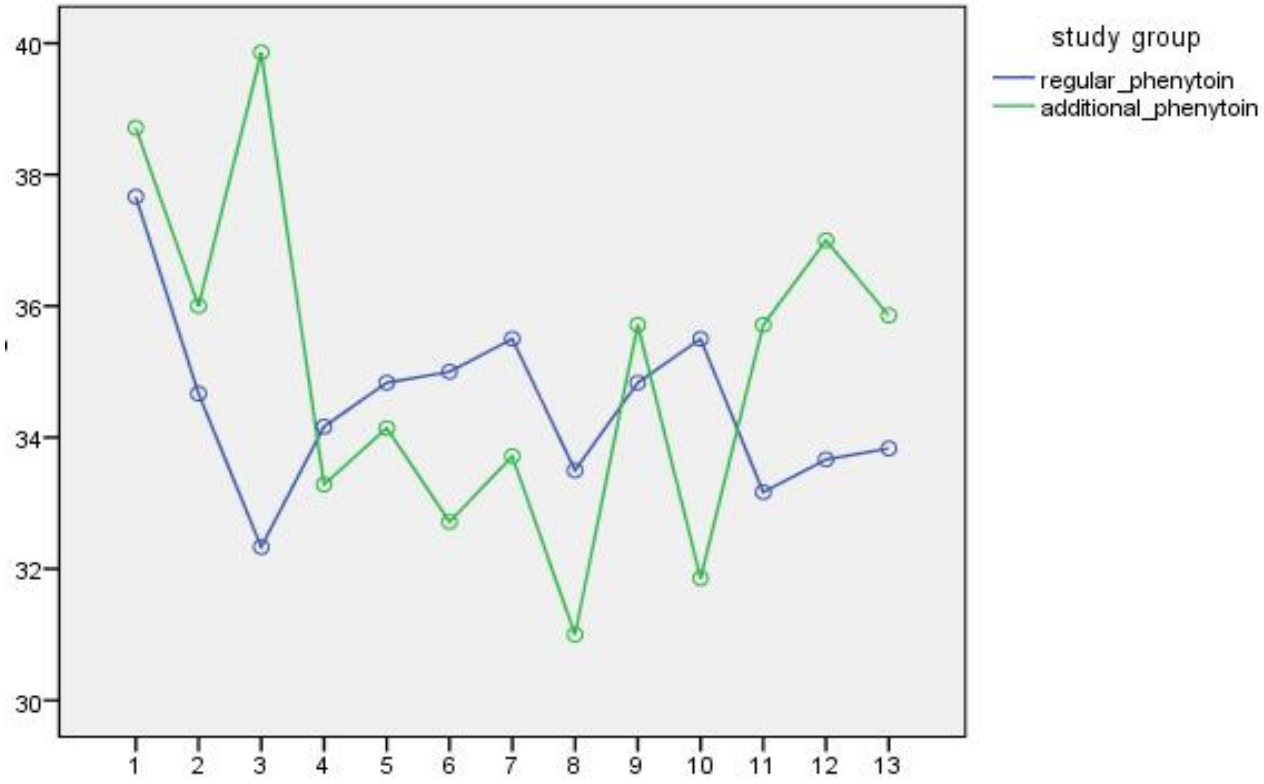
Y- axis: Mean blood pressure in mm Hg (MBP)

Effect of anticonvulsants on Bispectral index (BIS).

Since anticonvulsants can affect the depth of anaesthesia, the change in bispectral index (BIS) was noted across 1 hour during and after administration of anticonvulsant. It was measured using the bispectral index monitor.

Both, phenytoin and sodium valproate caused marginal drop in BIS during and within one hour of administration of an anticonvulsant. (Figure 13a ,13b).But there is no significant difference in BIS between patients who received additional Vs regular dose both clinically and statistically.

Figure 13a : Dot plot showing the Changes in BIS during and soon after administration of phenytoin.

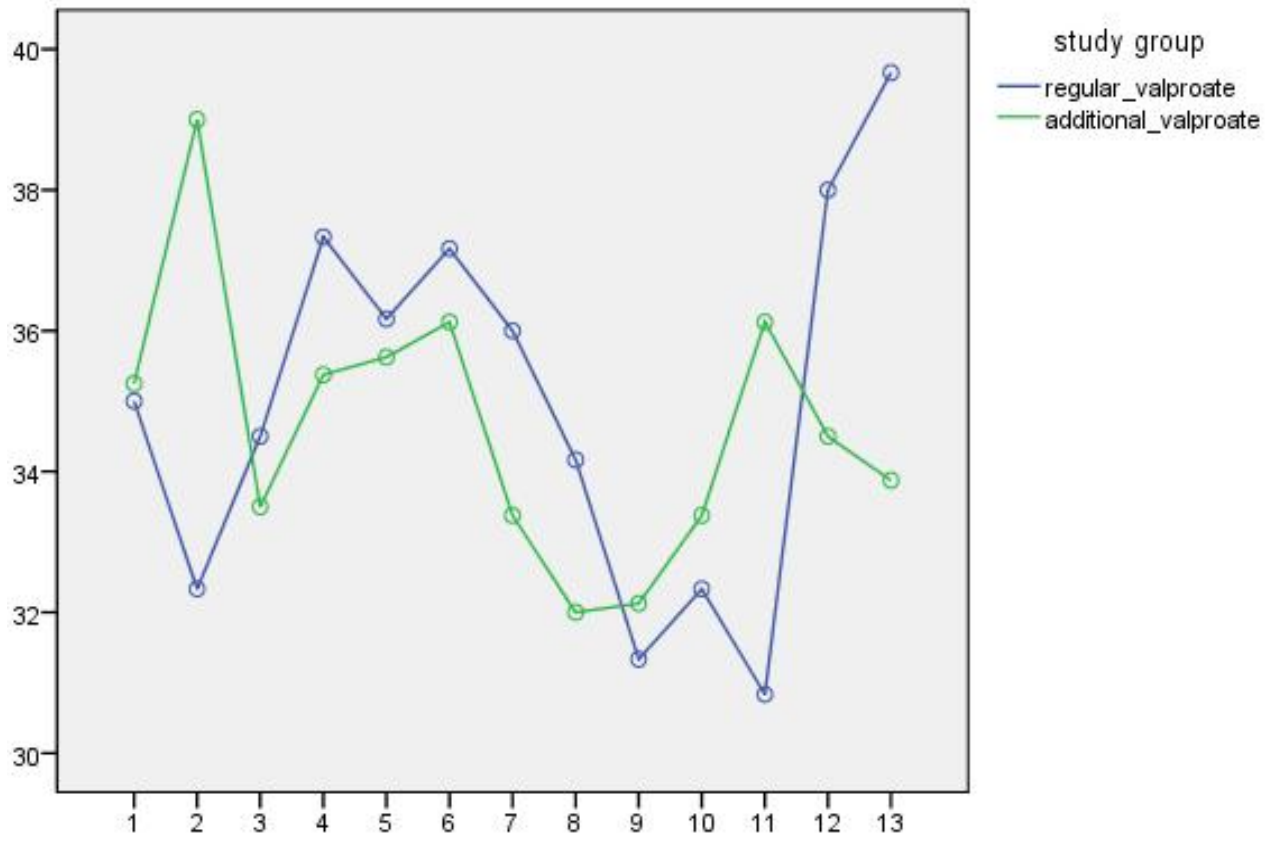


X - axis: Various time period of BIS measurement (1=baseline, 2=at 5min.3=10min….13=1hour,

Y- axis: BIS values (0-100)

In the Valproate group, the BIS values were measured in the same way. Across most time points the additional group had lower BIS values which is not significant.

Figure 13b : Dot plot showing the Changes in BIS during and soon after administration of Sodium Valproate.



X - axis: Various time period of BIS measurement (1=baseline, 2=at 5min.3=10min….13=1hour,

Y- axis: BIS values (30-50)

Requirement of Propofol and Fentanyl:

Requirement of propofol and fentanyl was almost similar between the two groups. Consumption of propofol was slightly higher in regular group but it is not statistically significant.

Table 6 : Showing the requirement of fentanyl and propofol between the two groups

	Regular group (Mean ± SD)	Additional group (Mean ±SD)
Fentanyl (µg)	260± 62.2	251±76
Propofol (mg)	296± 73	251± 65

Requirement of vasopressors to maintain haemodynamics:

The median value of phenylephrine was higher is the additional group 400 (150-800) when compared with the regular group 350(0-800).The median dose of noradrenaline in the additional group is 80 (0-340) while in the regular group it was 160 (0-200) as shown in Table 7 :

Table 7 : Showing the requirement of vasopressors between the two groups:

Vasopressors	Regular group Median (IQR 25-75)	Additional group Median (IQR 25-75)
Phenylephrine (µg)	350 (0-800)	400 (150-800)
Noradrenaline (µg)	160 (0-200)	80 (0-340)

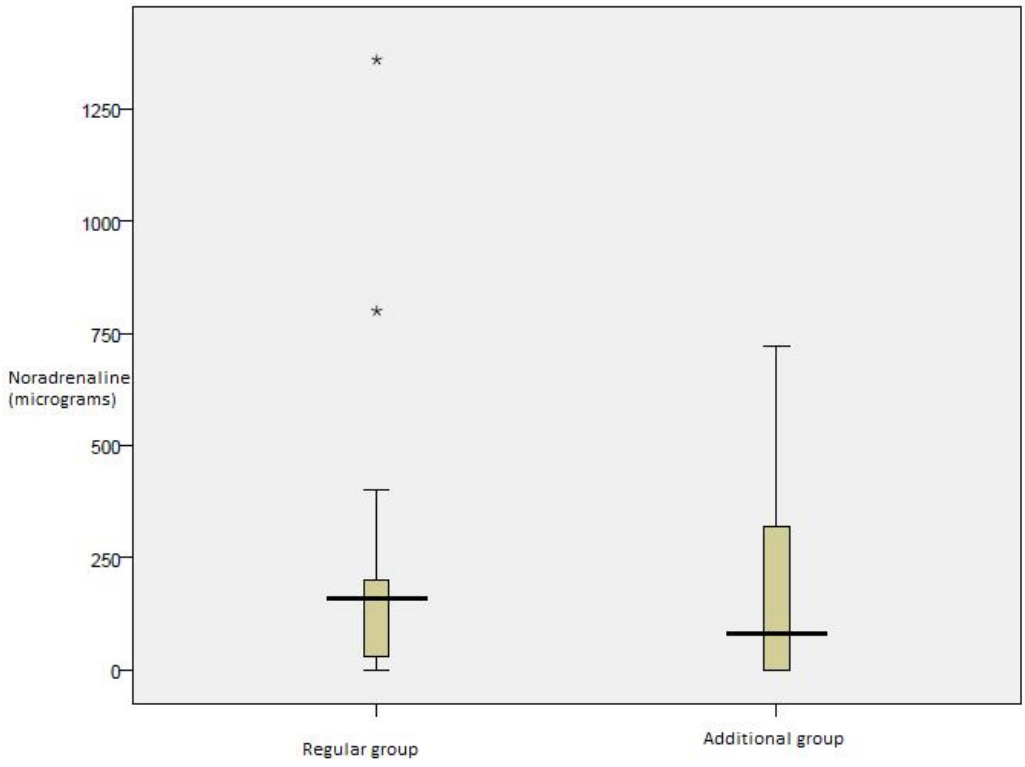


Figure 14a: Box plot showing the use of Noradrenaline in regular and additional group

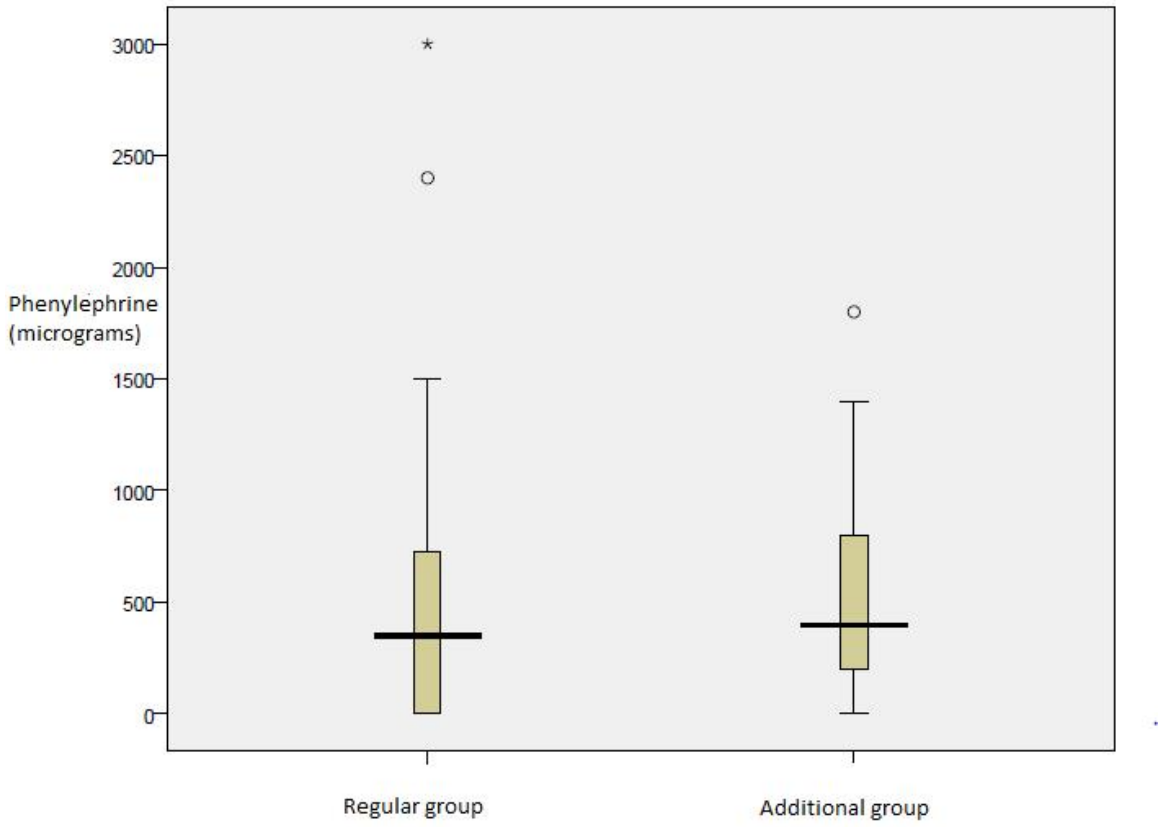


Figure 14b: Box plot showing the use of phenylephrine in regular and additional group.

Changes in anticonvulsant levels during craniotomy:

The rational for administration of bolus anticonvulsant during craniotomy, is that there is a possibility of declining plasma levels due to administration of intravenous fluid and blood / blood products during surgery. Lower plasma levels can lead to post craniotomy seizures because of multiple triggering factors during the immediate postoperative period such as cerebral edema, presence of post operative haematoma and brain contusion due to retraction. So we wanted to study the change in plasma level before and after craniotomy and correlate this change with IVF administration.

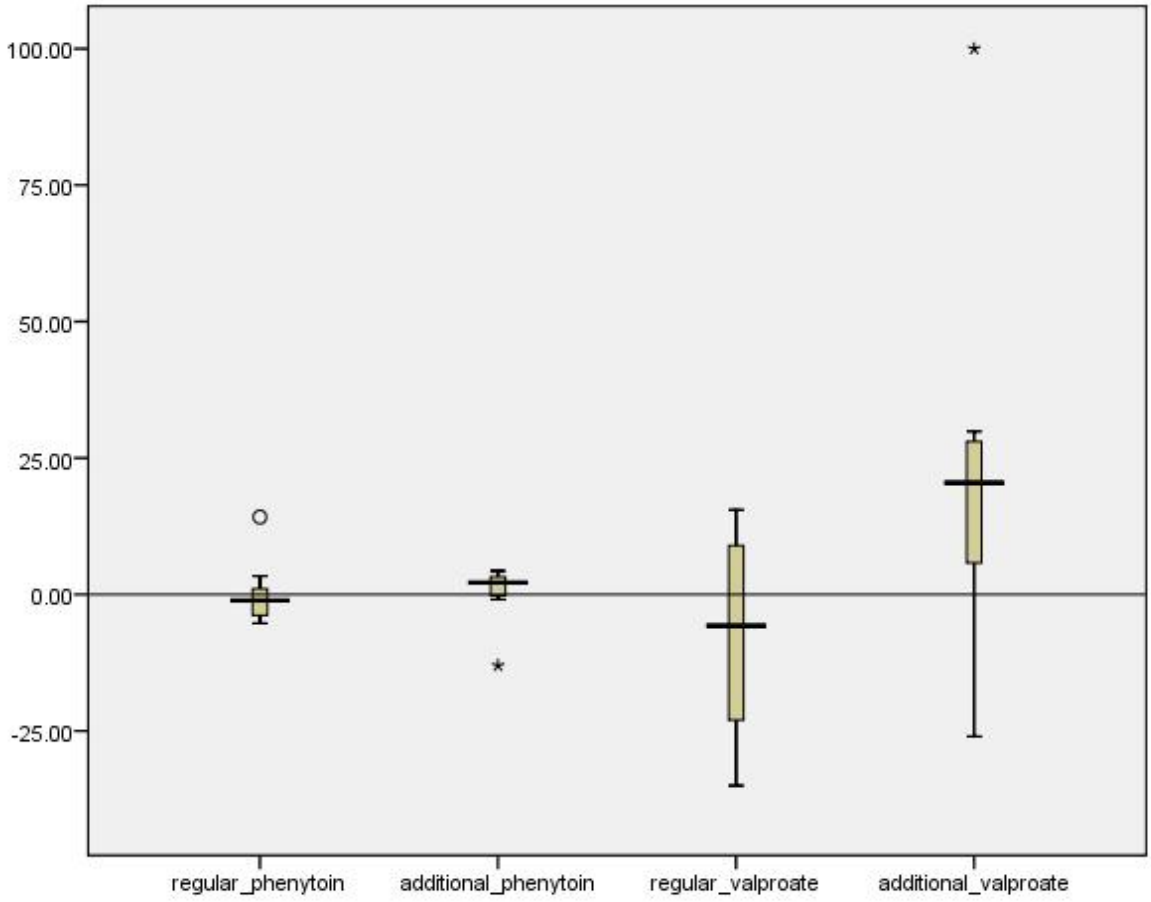
In the **regular Phenytoin group** the mean pre- induction plasma value was 10.03µg/ml and the post craniotomy value was 9.755µg/ml. The mean drop in anticonvulsant level was 0.27µg/ml. In the **additional Phenytoin group**, the mean pre-induction plasma level was 10.87 µg/ml and post craniotomy level of 10.824 micrograms/l showing a drop of only 0.05 micrograms/l. (Table 8)

In the **regular valproate group** the mean pre-induction plasma level was 78.47 µg/ml and post craniotomy mean levels were 70.87µg/ml, a mean drop was by 7µg/ml. In the **additional valproate group** the mean pre induction level was 60.79 µg/ml and post craniotomy was 80µg/ml, an increase by 20 µg/ml. (Table 8)

Table 8 : Showing change in plasma anticonvulsant level pre and post craniotomy.

Groups	**Regular dose**	**Additional dose**
Phenytoin (µg/ml)		
Pre-Surgery	10.03	10.87
Post surgery	9.755	10.824
Sodium Valproate(µg/ml)		
Pre surgery	78.47	60.79
Post surgery	70.087	80

Figure 15: Box plot Showing change in anticonvulsant level between the two groups for both Phenytoin and sodium valproate separately:



X axis: study groups

Yaxis: change in anticonvulsant level (postoperative plasma anticonvulsant level-preoperative anticonvulsant level)

In patients who received Phenytoin, despite anticonvulsant being started more than 14 days prior to surgery to maintain steady plasma levels only 31% had a therapeutic range, 57% had subtherapeutic level and 10% had supra therapeutic level.

In patients who received Valproate , 52% of patients had a therapeutic range, 30% had less than therapeutic range and 17% had above therapeutic range. At the end of craniotomy, 13% had less than therapeutic range, 70% had within therapeutic range and 17 % had above therapeutic range.

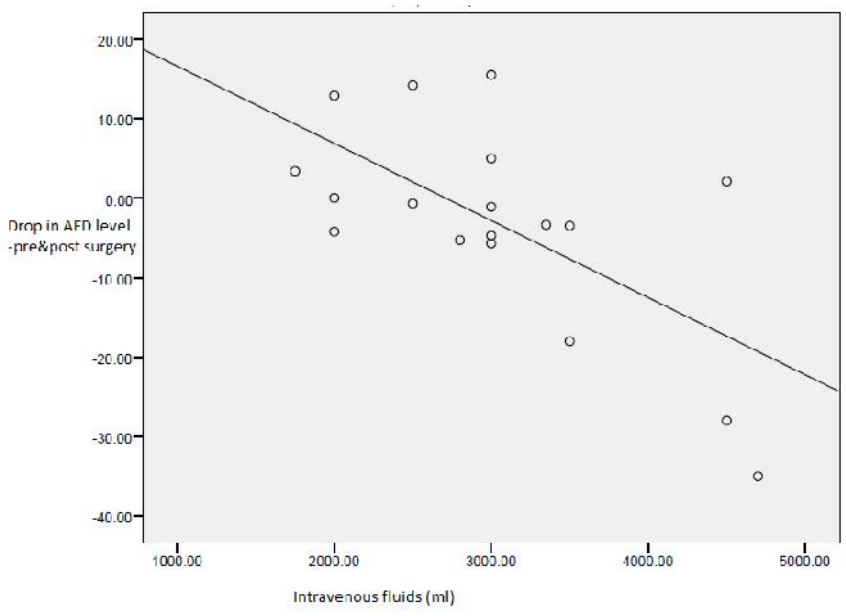
Table 9: Comparing the number of patients who had sub, therapeutic, supra therapeutic concentration of anticonvulsant before and after surgery.

Groups	Blood concentration	Pre surgery No of patients (Incidence)	Post surgery No of patients (Incidence)
Phenytoin (µg/L)	< 10 (Sub therapeutic)	11 (58%)	10 (56%)
	10-20 (Therapeutic)	6 (32%)	7 (39%)
	> 20 (supra therapeutic)	2 (10%)	1 (5%)
Sodium valproate (µg/L)	<50 (Sub therapeutic)	5 (30%)	2 (13%)
	50-100(Therapeutic)	9 (52%)	12 (70%)
	>100 (Supra therapeutic)	3 (17%)	3 (17%)

Correlation between IV fluids administered and drop in plasma anticonvulsant level:

In this study we found that there is a definite correlation between the amount of IVF administered and the drop in plasma anticonvulsant level, both in the regular as well as in the additional group. The drop was very significant in the regular group (p value 0.004) compared to additional group (P value 0.318). Figure 16a and 16b Scatter plot showing the correlation in regular and additional group respectively. As the blood loss increases, there is a definite decline in plasma level of anticonvulsant level.

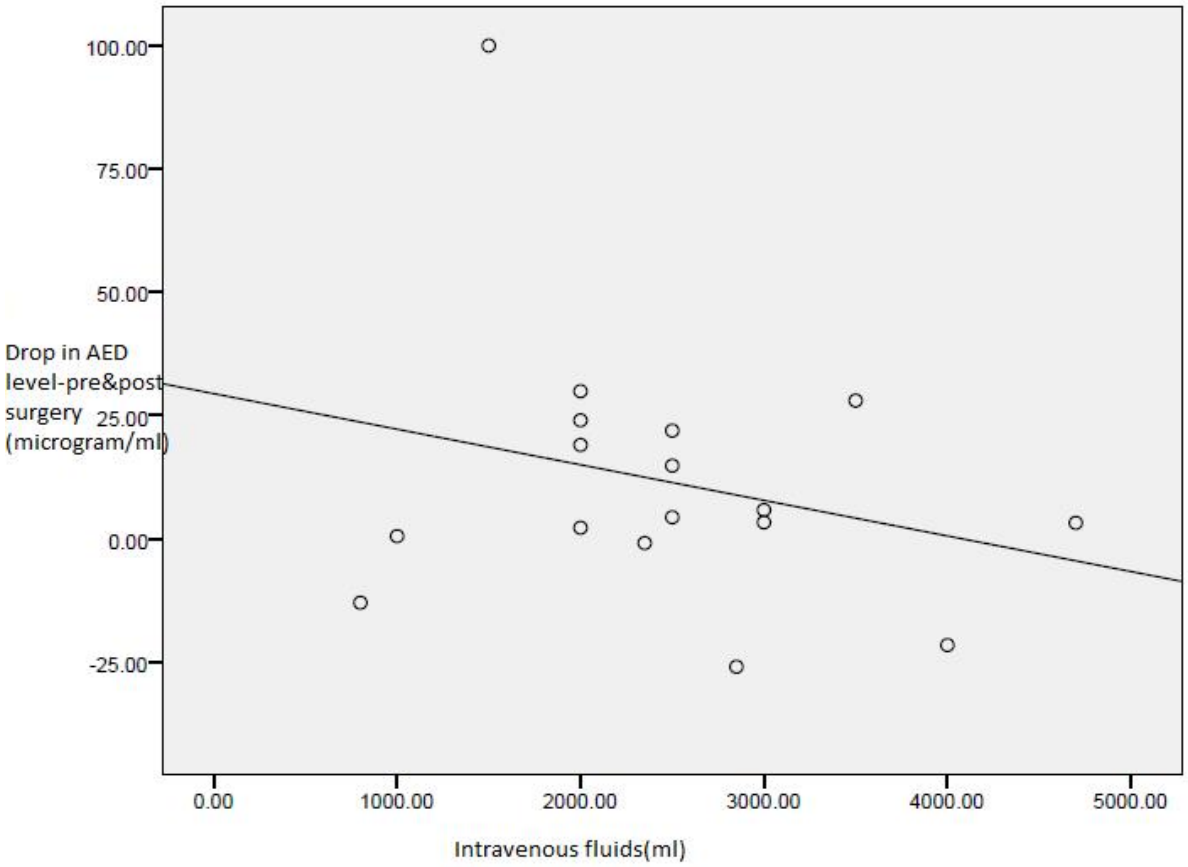
Figure 16a : Scatter plot showing the correlation between the drop in plasma anticonvulsant level and the amount of intravenous fluids administered in the Regular group.



X axis: Intravenous fluids in milliliters

Y axis: change in anticonvulsant level (postoperative plasma anticonvulsant level-preoperative anticonvulsant level)

Figure 16b : Scatter plot showing the correlation between the drop in plasma anticonvulsant level and the amount of intravenous fluids administered in the Additional group.



*AED=Antiepileptic drug

X axis: Intravenous fluids in milliliters

Y axis: change in anticonvulsant level (postoperative plasma anticonvulsant level-preoperative anticonvulsant

Effect of anticonvulsants on recovery from anaesthesia.

The recovery time for 3/ 36 patients were on the extreme range. This extreme range affected the mean value and the standard deviation. So, we have taken the median value with the interquartile range (IQR 25-75) for each parameter.

The time of ETT removal, time to open eyes on call, time taken to obey commands, time to orientation are shown in table with the median value and interquartile range (25-75). When we analyzed the results as two groups (additional Vs regular dose) there were no difference found between the two groups in all four parameters (Table 10).

Table 10 :Showing the recovery time between the regular Vs additional group.

Time	Regular group Median (IQR 25-75)	Additional group Median (IQR 25-75)	P value
Time to ETT removal(min)	15(13-20)	14(13-19)	0.75
Time to open eyes(min)	23(15-31)	24(16-27)	0.824
Time to obey commands (min)	33(25-45)	33(24-67)	0.824
Time to orientation(min)	42(35-53)	57(37-128)	0.208

We have done a subgroup analysis of recovery parameters in patients receiving Phenytoin and sodium valproate separately to see whether the drug has a significant impact on recovery. This subgroup analysis revealed patients who received additional Phenytoin had a significant delay in eye opening on call (22 min:26 min), time to obey commands (33min:48min) and time to get orientation (42min:120min) when compared to patients on regular dose group. Though this time difference is clinically significant, it was not statistically significant.

Interestingly, in the sodium valproate group, we did not find any significant difference both, clinically or statistically between the regular Vs additional dose group.

Table 11 : Showing the subgroup analysis of recovery parameters between the Phenytoin and sodium valproate group.

Recovery parameters	Phenytoin Median (IQR 25-75)		Sodium Valproate Median (IQR)	
	Regular	Additional	Regular	Additional
Time to ETT removal (min)	16 (13-19)	14 (13-15)	14 (12-21)	17(12-21)
Time to open eye on call (min)	22 (15-29)	26 (18-38)	30 (13-48)	21(14-26)
Time to obey commands (min)	33 (25-44)	48 (30-120)	37 (21-53)	31 (20- 48)
Time to orientation (min)	42 (35-52)	120 (39-210)	42 (35-53)	51(31-102)

Incidence of post operative seizures:

Despite being on prophylactic anticonvulsant before craniotomy 5 out of 36 developed post operative seizures.1 patient in regular phenytoin group, 1 patient in the additional phenytoin group, 1 patient in the regular Valproate group and 2 patients in the additional Valproate group.(Table 12)

Table 12: Incidence of seizures in each of the groups

Group	Regular Group No of pts (incidence %)	Additional Group No of Pts (Incidence %)
Phenytoin	1/12 (8.3%)	1/7 (14.3%)
Sodium valproate	1/7 (14.3%)	2/10 (20%)

Out of 2 patients who had post operative seizures in regular group, one had sub therapeutic level and one had normal therapeutic level during the post operative period. Out of 3 patients in the additional group one had sub therapeutic, one had normal therapeutic level and the other one had supratherapuetic level.

DISCUSSION

This study was undertaken to assess whether an additional dose of anticonvulsant administered during surgery has an impact on recovery from anaesthesia, intraoperative haemodynamics, depth of anaesthesia, on plasma anticonvulsant level and the incidence of post operative seizures.

We found more females in patients who received sodium valproate compared to Phenytoin. This difference may be due to the fact that the incidence of Steven Johnson syndrome is higher in female patients who are diagnosed with meningioma who were on Phenytoin. So Phenytoin is not generally given to female patients with suspected meningioma. The exact cause for this skin reaction is not known. Meningioma was the commonest tumour in both, regular as well as the additional group.

Recovery from anaesthesia:

There are various factors which can alter the recovery from anesthesia in a neurosurgical case such as age, tumor pathology, location, brain retraction, and presence of cerebral edema and so on. In our study, we had carefully selected patients in both groups so that the distributions of age, tumour type, location and tumour volume all were equal. Also, most patients had surface tumour of less than 4 cm in size so, the chances of brain retractions and brain edema induced delayed recovery is very minimal in both the groups.

There are various anaesthetic factors which can cause delay in recovery. The intraoperative factors which can cause delayed awakening such as hypoxia, hypercarbia, hypo or hyperglycemia, hypothermia, acute hyponatremia all were avoided and ruled out in every patient. Even long duration surgeries (> 5 hrs) can affect the recovery, in this study if the surgical duration is more than >5 hours we had excluded those patients. There was no difference in duration of anesthesia between the two groups.

Our study was the first one, to study the effect of anticonvulsant on recovery from anaesthesia. We had measured the anticonvulsant level pre and post surgery and correlated it with the recovery time. Since it was possible only, to measure the plasma level of Phenytoin and sodium valproate we had taken patients who were on those anticonvulsants. In this study we have found that the administration of bolus phenytoin increased the recovery time to obey commands by >15 min and increased the orientation time by > 1 hour when compared to regular dose group. Aggressive use of an anticonvulsant can also cause delay in awakening. There were 5 patients whose recovery time (Time to orientation) was > 2 hours, those plasma levels were within the therapeutic range. This can be explained by the sedative and hypnotic effects of phenytoin even in therapeutic range causing delayed recovery. There are reports of acute administration of Phenytoin causing delayed recovery in the literature (15). Few studies have shown that long term administration of Phenytoin causing cognitive dysfunction(3).

On the other hand there is no significant delay in recovery of patients who received additional valproate when compared to regular group. This may be due to the fact that sodium valproate has less sedative and hypnotic effect compared to Phenytoin(3)(16).

Haemodynamics:

Phenytoin is a class I b anti-arrhythmic and it blocks the sodium channels in the cardiac tissue and causes sinus arrest and junctional bradycardia(14). Intravenous Phenytoin administered at the rate of > 50mg/min is not advised for the above reason. There are case reports of oral phenytoin causing sinus bradycardia and asystole are available in the literature (14) In this study, we had administered the anticonvulsant during the start of first burr hole time over a period of 20 mins. The drugs were administered during the bone flap removal so that the change in haemodynamics is attributed only to the drug effect because of minimal stimulation during this time period. The heart rate change was observed while administering both regular as well as the bolus dose of Phenytoin. The drop in heart rate was more in the additional Phenytoin group as expected because of its anti-arrhythmic effect. In Valproate group there appears to be an increase in heart rate over time in the additional group when compared to the regular group. This can be explained by its minimal effect on heart rate.

In the additional Phenytoin group, the mean arterial pressures was lower and amount of vasopressors used to maintain stable haemodynamics were higher proving that Phenytoin caused more haemodynamic fluctuations. In our study, we found that the influence of Valproate on haemodynamics was less apparent even in additional group. This was proven by the fact that the need for vasopressors is also less with use of sodium valproate. It has been reported that compared to Phenytoin, sodium valproate causes less haemodynamic instability such as hypotension and bradycardia. A study published by eHealth me on adverse effect of sodium valproate on > 12,000 patients and found the incidence of hypotension was only 2.8% which was updated on August 2015. But, there are case reports of hypotension caused by sodium valproate are also reported in the literature(17). In these reports, the patients were very old (>70 yrs) or very young (<10 yr) this could the reason for hypotension.

The sedative properties of anticonvulsants can increase the depth of anaesthesia as measured by the bispectral index (BIS) monitor and it may be one of the reasons for delayed recovery from anaesthesia. A study done by Gokben Hizli et al showed that decrease in the amount of Propofol needed to reach a BIS value of 60 in patients who were pre-treated with Valproate for bipolar affective disorder (BPAD) during electro convulsive therapy (ECT)(18). Study by Bithal PK has shown that preoperative administration of Phenytoin increases the anesthetic depth which was monitored by BIS and also reported that it reduces the haemodynamic response to laryngoscopy and intubation(19).In our study we have noted that there is a marginal decrease in

BIS numbers while administration of both anticonvulsants. But the drop was not significant between the regular group and the additional group.

Incidence of post operative seizure:

The American academy of neurology guidelines (2002) suggested that prophylactic anticonvulsants for craniotomy is not effective in preventing the first episode of seizures post craniotomy. (2) In our study a total of 5 patients had seizures in the immediate post operative period. These five patients were analyzed in detail.

The first patient presented with seizures and was started on Phenytoin 100 mg three times daily 60 days before surgery and was continued intraoperatively. The pathology was an epidermoid tumor, and her pre-craniotomy plasma level and the post craniotomy level was 2.5 µg/ml and 4.65 µg/ml respectively. The second patient had a frontal meningioma and did not present with seizures preoperatively, was started on Valproate 500 mg two times daily which was continued intraoperatively, her pre, post craniotomy plasma level of Valproate was 75 µg/ml and 44 µg/ml which is lesser than the therapeutic range. The third patient had a frontal cavernoma and presented with one episode of seizure. She was started on Valproate 14 days prior to surgery and her pre craniotomy Valproate level was 66 µg/ml, was given an additional 500 mg of Valproate during craniotomy, post craniotomy plasma value was 90 µg/ml, well within therapeutic range. But she had multiple episodes of post operative seizures and was re-explored was found to have a residual tumor. The

fourth patient underwent a frontal craniotomy for frontal meningioma, had seizures preoperatively was on Valproate for 11 days prior to surgery was given 900mg valproate intraoperatively. Her pre and post craniotomy Valproate level was 76µg/ml and 104µg/ml. Fifth patient had a temporal epidermoid who presented with pre operative seizures was started on Phenytoin preoperatively was given a bolus of phenytoin 300mg intraoperatively, her plasma values were 8 and 10 µg/ml at end of surgery.

Out of 5 patients who had post operative seizures 4 of them had presented with preoperative seizures. So it is one of the major risk factors for developing post operative seizures. Out of 5 patients who developed post operative seizure, 2 of them had subtherapuetic plasma level. We did not find correlation between the plasma level and occurrence of post operative seizures. Since our sample size was too small we cannot comment on plasma level and the occurrence of post operative seizures.

In our study we found that despite of starting the anticonvulsant more than two weeks prior to surgery, 58% patient who were taking Phenytoin had sub-therapuetic level. Our study results were almost correlating with study done by Uma maheswara Rao et al in which they have showed that despite of starting preoperative phenytoin 7 days prior to surgery, 50% of patients had subtherapeutic levels (11). We have found that compared to Phenytoin, only 30 % patients had subtherapuetic level in those who received sodium valproate.

We have also found that there was a strong correlation between the amount of IVF administered and decline in plasma level. Also there was a strong correlation between the amount of blood loss and decline in plasma level.

Limitations

1. One of the major limitations of our study was small sample size. So, our study results have to be interpreted with caution. We are planning to continue the study in future to increase the sample size and the power of the study. Then our results can be interpreted better and can bring about a change in clinical practice on day to day basis.

2. Our primary outcome was to see whether administration of additional anticonvulsant delays the recovery from anaesthesia. Main surgical reason for delayed recovery while operating the superficial lesions is cerebral edema. We did not do CT brain to rule out cerebral edema or presence of residual tumour or tumour bed haematoma for all patients who had delayed recovery.

3. For those patients who had focal seizure in the immediate post operative period, midazolam was administered which further delayed recovery time.

Strengths

1. This study is the first one to compare the recovery time from anaesthesia in patients receiving a regular dose of an anticonvulsant with those patients who received an additional dose.

2. We had selected the patients carefully to rule out surgical and non surgical confounders to our best of our ability and carried out the study so that delay in recovery can be attributed to anticonvulsant.

3. To our knowledge, this study is the first one to compare the correlation of amount of IVF administered and decline in plasma level of anticonvulsant.

CONCLUSION

Administration of additional dose of Phenytoin causes delay in recovery, haemodynamic fluctuation during surgery. Administration of additional dose of sodium valproate did not affect either the recovery time, or the haemodynamics. Presence of preoperative seizures is one of the significant risk factor for developing post operative seizure. Since there is a correlation between the amount of IVF administered, blood loss and the decline in plasma level of anticonvulsant, administration of an additional anticonvulsant in patients who are resuscitated with large amount of IVF will definitely help to restore the plasma anticonvulsant level. Due to the small sample size, it is very difficult to comment on occurrence of post operative seizures and the plasma anticonvulsant level. This warrants larger randomized control trial to see the correlation statistically. This study gave us an insight into a probable reason for delay in recovery post craniotomy.

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PATIENT INFORMATION SHEET

NAME OF STUDY: ANTIEPILEPTIC DRUG LEVELS AND ITS EFFECT ON WAKING UP FROM ANAESTHESIA IN PATIENTS UNDERGOING BRAIN TUMOUR SURGERY

WHAT IS EPILEPSY?

Brain tumours and surgery for brain tumours can cause seizures . Seizure or epilepsy is a disorder of abnormal electrical activity in the brain leading to abnormal and involuntary movement in a part or whole body. Seizures can cause a state of unconsciousness, biting of the tongue and bleeding, aspiration, decreased oxygen in the brain and brain swelling.

WHAT ARE ANTIEPILEPTIC DRUGS?

Antiepileptic drugs are drugs given to prevent seizures/fits. Commonly used drugs are Phenytoin, sodium valproate. These drugs are usually given to patients undergoing a surgery for brain tumour removal in certain areas of brain.

WHY SHOULD IT BE GIVEN BEFORE SURGERY FOR BRAIN TUMOURS?

Surgery for brain tumour removal involves opening the skull bone and removing the tumour from the brain. This surgery itself or even the brain tumour can cause seizures therefore these drugs are given to prevent seizures especially during and after the surgery

WHAT IS GENERAL ANAESTHESIA?

General anaesthesia is a type of anaesthesia in which you will be given medicines to remain unconscious throughout the period of surgery to be unaware of surgery and pain produced during surgery. Once you are made unconscious, you will not remember any event occurring in that surgical time. During this period your blood pressure, heart rate, blood oxygen levels etc will be continuously monitored and get treated by the attending anaesthesiologist if needed. At the end of surgery, you will be again woken up and will be shifted to ICU once you completely recover from anaesthetic effects.

WHAT WILL BE DONE AS A PART OF THIS STUDY UNDER ANAESTHESIA?

In our study, we want to see and compare whether administration of extra dose of same antiepileptic drugs what you are receiving has an added effect on anaesthetic medicine. We also want to measure the blood level of antiepileptic drug after giving the additional dose to see if it has an impact on waking up from surgery. You will be given General anaesthesia for the surgery. You will receive all the medication as per our standard of practice. Additionally, we will put one electrode on your forehead to monitor the depth of your sleep during the entire surgery.

In our study we are dividing the patients in to two groups, Group 1 and Group 2. Group 1 patients will receive extra dose as per surgeon's preference and group 2 patients do not receive any additional dose but you will receive the regular dose.

During anaesthesia all vitals will be monitored and documented as a routine protocol. Depth of your sleep also will be monitored during surgery. Two blood samples will be taken, one in the beginning and one at the end of surgery to check the blood levels of antiepileptic drugs. At the end of anaesthesia, time taken for you to wake up will also be noted down and will be compared with blood levels of your antiepileptic medication. Post operative seizure occurrence will also be documented.

WILL THERE BE ANY ADDITIONAL COST INVOLVED?

Cost of blood tests will be borne by the study. Confidentiality will be maintained at all times.

WHAT ARE THE RISKS AND BENEFITS TO ME IF I TAKE PART?

There are no risks to being a part of the study. There are no additional invasive procedures/discomfort involved in this study .By being a part of this study benefits is anticonvulsant levels will be monitored and the adequacy of current dosing regimens during surgery can be assessed.

NUMBER OF PARTICIPANTS INCLUDED IN THIS STUDY AND RESPONSIBILITIES

As a part of this study a total number of 40 patients will be included. After anaesthesia has been administered one blood sample will be taken and a second sample after surgery. Recovery from anaesthesia will be assessed every 15 minutes until the participant is fully oriented and obeying commands. The participant will be monitored for the next 48hours for any episode of seizures.
participation is voluntary and the participant may withdraw from the study at any point , refusal will not involve any penalty or loss of benefits to which the participant is otherwise entitled.

Contact:
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christian medical college
vellore
phone number :9626150062

DATA SHEET:

TITLE OF STUDY: An observational study comparing the recovery time in patients receiving additional anticonvulsant dose intraoperatively Vs those receiving regular dose during supratentorial craniotomy.

DEMOGRAPHY

NAME	
HOSPITAL NUMBER	
AGE	
SEX	
DIAGNOSIS	

PREOPERATIVE DETAILS

SEIZURE HISTORY: GTCS/ PARTIAL

ANTICONVULSANT CURRENTLY IN USE: PHENYTOIN/ VALPROATE

DOSING SCHEDULE

TIME					
DOSE					

DURATION SINCE START OF ANTIEPILEPTIC THERAPY:

COMORBIDITIES: Diabetes/ Hypertension/ Asthma/ Ischemic heart disease

INTRAOPERATIVE DATA

ANTICONVULSANT ADMINISTERED INTRAOPERATIVELY:

TIME OF ADMINISTRATION:

DOSE ADMINISTERED:

HEMODYNAMIC CHANGES DURING ANTICONVULSANT ADMINISTRATION

TIME	0(BEFORE AED)	5MIN	10MIN	15MIN	20MIN	30MIN	35MIN	40MIN	45MIN	50MIN	55MIN	1HOUR
HEART RATE												
SYSTOLIC												
DIASTOLIC												
MEAN												
BIS												
MAC												

NEED FOR VASOPRESSORS PNP/NORAD- DOSE

TOTAL DOSE OF FENTANYL GIVEN (including the induction dose) :

TOTAL DOSE OF PROPOFOL GIVEN (including the induction dose):

DURATION OF SURGERY: DURATION OF ANAESTHESIA:

BLOOD LOSS DURING SURGERY:

IV FLUIDS ADMINISTERED

CRYSTALLOID	
COLLOID	
BLOOD	
BLOOD PRODUCTS	

EXTUBATION

Time of stopping isoflurane		**DURATION**
Time of removal of ETT (Extubation time)		
Time of Eye opening on call		
Time of obeying command (squeezing examiners hand, bending legs)		
Time to get oriented to person and place (what is your name ? and Which hospital are you in?		

POST OPERATIVE DATA:

Pre op plasma anticonvulsant level:

Post op plasma anticonvulsant level:

Episodes of seizure in 48hrs: **Yes/ No** **Number of episodes :**

Time taken for obeying commands and orientation to person and place in ICU.

Parameter	At arrival	At 15 min	At 30 min	At 45 min	At 1hr	1:15	1:30	1:45	2hr	2:30min	3hour	3:30min	4 hours
Time taken to obey command (squeezing hand, bending legs)	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No
Time to get oriented to person and place (What is your name?, What is the name of the hospital)	Yesno	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes no	Yes no	Yes no	Yes No	Yes No

Informed Consent form to participate in a research study

1. **Study Title: AN OBESERVATIONAL STUDY COMPARING THE RECOVERY TIME IN PATIENTS RECEIVING ADDITIONAL ANTICONVULSANT DOSE INTROPERATIVELY VS THOSE RECEIVING REGULAR DOSE DURING SUPRATENTORIAL CRANIOTOMY.**

Study Number: _____

Subject's Initials: _____ Subject's Name: _____

Date of Birth / Age: _____

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the investigators of the clinical trial, others working on the Investigators behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: _____/_____/_____

Signatory's Name: _____ Signature:

Or

Representative: _____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature or thumb impression of the Witness: _____

Date: _____/_____/_____

Name & Address of the Witness: _____

_____